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ACTION POTENTIALS OF MUSCLES IN "SPASTIC" CONDITIONS

PAUL F. A. HOEFER, M.D.
AND
TRACY J. PUTNAM, M.D.
NEW YORK

The term "spasticity" in this report is used to describe the clinical picture produced by extensive lesions mainly of the corticospinal motor systems, and in some instances presumably also of other motor systems, subcortical in origin. "Spasticity" thus has to be distinguished from "rigidity," which in association with tremor, or occasionally without it, is seen (among other phenomena) in Parkinson's disease, and also from "decerebrate rigidity." An attempt will be made later to clarify the interrelationships of these conditions, which have not been clearly distinguished by older neurologists.[1]

It has not been possible to include in this investigation the study of flaccid paralysis following lesions of the brain and long tracts. This syndrome, rarely seen as a permanent state in man, has not been observed in our series of cases. It has been studied in subhuman primates especially by Fulton and his co-workers,[2] who ascribed the syndrome to lesions of the pyramidal tract alone.

At some future date the methods here used may be employed to study the results of similar known circumscribed lesions in human beings. For the present investigation material has been taken as it became available.

This is the second of a series of clinical and experimental studies of motor disorders.

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From the Department of Nervous and Mental Diseases, Harvard Medical School and the Neurological Unit, Boston City Hospital.

1. Gowers, W. R.: A Manual of Diseases of the Nervous System, ed. 2, London, J. & A. Churchill, 1893, vol. 2. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 5, Berlin, S. Karger, 1908.

2. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938; Spasticity and the Frontal Lobes, New England J. Med. **217**:1017, 1937.

The "spastic" syndrome seen in all the patients studied here consists of paralysis or motor weakness associated with a loss of finer movements, increase of muscular resistance to passive movements (especially to extension of the arm and flexion of the leg), increase of proprioceptive (tendon) reflexes, clonuses and signs of the Babinski group. In addition to these findings, most of the patients showed spreading of proprioceptive reflexes. Some presented atrophies and fibrillations. Occasionally, involuntary movements of the "spinal withdrawal" pattern were seen.

It has been found possible to understand certain features of normal innervation of skeletal muscles from an analysis of the action potentials.[3] It seems justifiable, therefore, to assume that any specific features of the action potentials traced from muscles in cases of spasticity may be an indication of a specific mode of innervation rather than a mere sign of activity.

An essential first step toward a physiologic interpretation of any electromyographic data is a consideration of the properties of the single impulse as it is transmitted to the muscle. This has been attempted for normal human muscle in a previous investigation.[3b] With the apparatus at present available, it has been impossible to secure satisfactory tracings of the single spike potential or to determine its refractory period. This part of the investigation of abnormal types of innervation must therefore be postponed. Indirect evidence exists, however, to show that there is no essential difference in character, range of amplitude or time relations between records of individual discharges taken from normal and those taken from spastic muscles.

The next question is: What constitutes the peculiar character and the weakness of voluntary movement in patients with spastic states? How much innervation reaches the spastic muscle; where does it originate, and how does it manage both the whole muscle and its constituent motor units?

A third question is concerned with the properties of the increased reflexes in spasticity and with the nature of clonus. Here, again, the relation of the motor units to the whole muscle is of particular interest. Consideration of spontaneous clonuses, i. e., clonuses occurring without obvious external stimulation, leads to a fourth question, namely: What occurs during involuntary spontaneous movement, such as fibrillary and fascicular twitches and mass movements of the "spinal withdrawal" pattern?

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3. (*a*) Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Normal Subjects, Arch. Neurol. & Psychiat. **42**:201 (Aug.) 1939. (*b*) Hoefer, P. F. A.: Versuche über Nervenaktionsströme: II. Nerv-Muskel-Beziehungen, Ztschr. f. Biol. **93**:335, 1933.

4. Footnote deleted.

Increased resistance to passive movements, spasticity proper, will have to be considered, and an attempt should be made to differentiate it from other phenomena of spasticity. Finally, the influence of drugs which might prove useful in an attempt to institute rational therapy on a basis of physiologic understanding of the disturbed function of muscles in spasticity will be discussed, if only briefly, in the present report.

MATERIAL AND METHODS

Twenty-four patients were studied in this investigation. Clinical data concerning them are presented in table 1.

TABLE 1.—*Clinical Data on Patients with Spastic Conditions*

Current No.	Patients' Initials	Diagnosis
1	J. R.	Syringomyelia
2	H. L.	Hemiplegia
3	M. F.	Diffuse encephalitis
4	K. B.	Tuberculous abscess, spinal cord
5	J. T.	Diffuse arteriosclerosis
6	G. D.	Hemiplegia
7	R. S.	Multiple sclerosis
8	R. H.	Meningovascular syphilis (epileptic seizures)
9	F. H.	Amyotrophic lateral sclerosis
10	F. O.	Cervical hematomyelia
11	V. H.	Neuromyelitis optica
12	A. M.	Hemiplegia following extensive resection of left hemisphere
13	J. L.	Suspected tumor of cord
14	E. M.	Multiple sclerosis
15	C. G.	Amyotrophic lateral sclerosis
16	W. S.	Multiple sclerosis
17	D. N.	Tumor of cord
18	G. J.	Multiple sclerosis
19	E. H.	Multiple sclerosis
20	J. F.	Multiple sclerosis
21	H. B.	Transverse myelitis
22	W. A.	Amyotrophic lateral sclerosis
23	A. T.	Syringomyelia
24	E. D.	Hemiplegia following injury to head

The records were taken with a cathode ray oscillograph and, whenever simultaneous tracings were desired, with a six channel, ink-writing oscillograph.[5] Surface electrodes and pairs of coaxial needle electrodes inserted into the muscle were employed. The methods used have been described in detail in a previous report.[3a]

RESULTS

ACTION POTENTIALS DURING VOLUNTARY CONTRACTION

Motor power developed in voluntary contraction of spastic muscles is usually much diminished, though the muscles are well preserved. Thus, the maximum of strength for grip in the spastic right hand of a patient as tested with a dynamometer was 13 Kg., while the strength of squeeze of normal right-handed

5. Dr. W. G. Lennox and Dr. F. A. Gibbs permitted use of the ink-writing oscillograph.

Dr. A. Forbes and Dr. H. Davis made valuable suggestions and criticisms in the manuscript of this report.

subjects measures 45 Kg. or more (fig. 1 *C*). Action potentials recorded in surface leads during maximal voluntary innervation of a muscle are seen in figure 1. Tracings were made from extensor and flexor muscles of the upper portion of the arm, the forearm, the thigh and the calf. This selection includes those muscles which produce the characteristic posture of spastic hemiplegia, namely, the flexors of the arm and the extensors of the leg, and their respective antagonists. The action potentials have a characteristic appearance. The spikes are much smaller and also less frequent than normal, with the exception of those obtained from the "antigravity muscles" in some instances in which the patients were able to support the weight of the body in walking in spite of marked hemi-

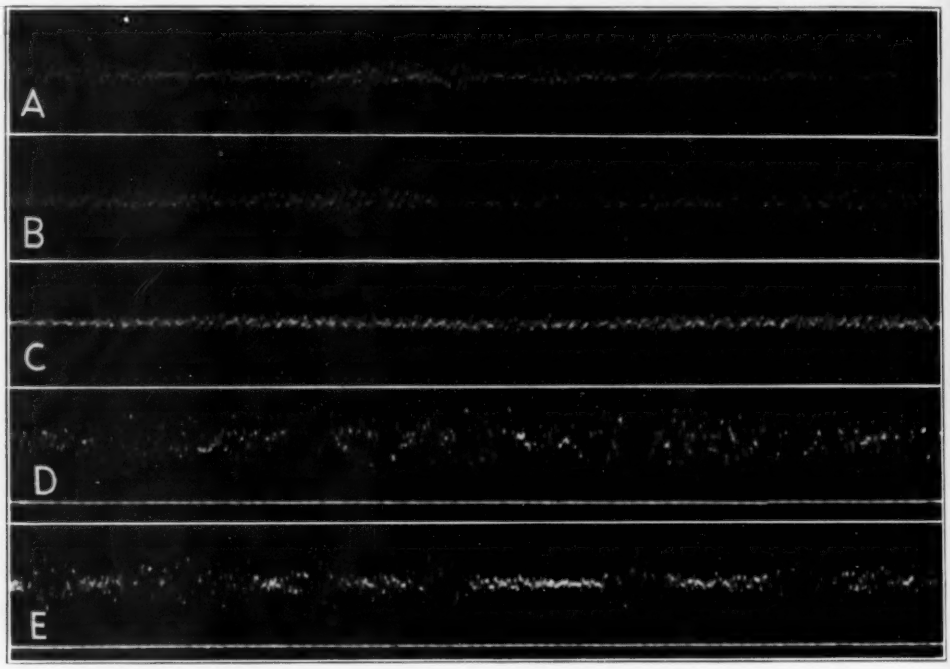

Fig. 1.—Voluntary contraction of spastic muscles in surface leads. Time: one-sixtieth second between flashes. Calibration: 3.3 mm. per hundred microvolts. Cathode ray oscillograph.

A and *B* (patient 10, Sept. 8, 1938): Right rectus femoris, two successive innervations. Note grouping of spikes, particularly in *A*.

C (patient 20, July 25, 1938): Flexor group of right forearm.

D and *E* (patient 6, January 14, 1937): Musculature of right calf. Two runs, from the height and toward the end of innervation, respectively. Note height, frequency and grouping of spikes.

plegic spasticity (fig. 1 *D* and *E*). Even in such cases, spike frequencies and amplitudes are comparatively low. In addition, the pattern of almost all tracings is markedly uneven, with tendencies toward interruption of the sequence of impulses and with formation of groups at regular intervals, even in the muscles

which were apparently the strongest of those studied. The maximal frequencies in the records shown are below 200 per second, with the exception of that from the calf musculature, in which the frequency varies between 260 and 320 per second. The difference between the amplitudes of spikes recorded from contraction of spastic muscles and of those recorded during normal voluntary contraction is much more marked than the difference between the frequencies seen in the two conditions, respectively.

In another group of observations the relation of motor units of a single muscle to each other was studied during moderate effort. The ink-writing oscillograph was used to trace motor unit records in simultaneous independent leads. Eight experiments were carried out, in which three pairs of coaxial electrodes were

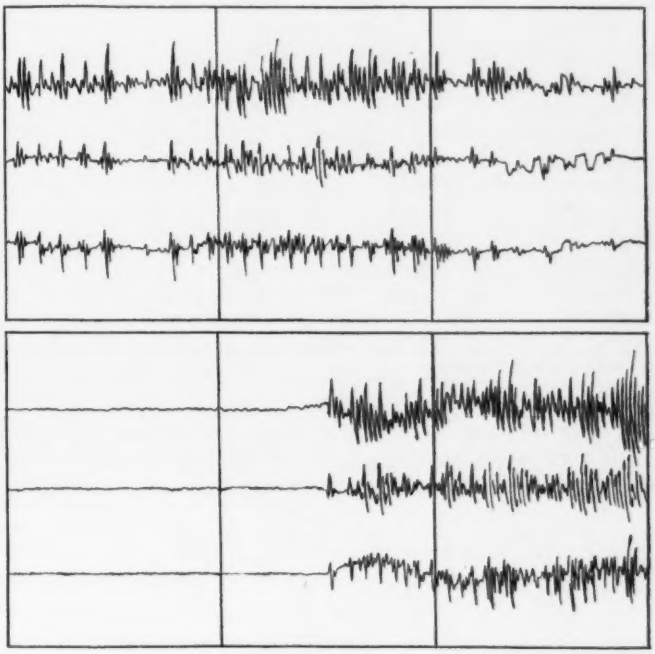

Fig. 2.—Two records showing voluntary contraction of a spastic left rectus femoris muscle in simultaneous coaxial needle leads (patient 20, July 27, 1938). Time: one second between vertical lines. Calibration: upper tracing in both records 6 mm. per hundred microvolts; other two tracings 4 mm. per hundred microvolts. The difference is incidental. Note tendency to synchronization of all three leads; note synchronous start in lower record; note also complete electrical inactivity during rest, before onset of contraction in lower record. Ink-writing oscillograph.

inserted into unanesthetized muscle. The same muscle groups were studied as in the experiments on whole muscles already described. Records from one of the observations are seen in figure 2. Spike frequencies per second counted for three simultaneous independent leads from 2 patients are presented in tables 2 and 3.

In all instances the patterns thus recorded with independent leads are found to be almost identical. There is a high degree of synchronization both in patterns and in frequencies. This is carried out in even smaller details in patterns, while in frequencies there is a moderate variation at times. The discharges recorded from several motor units start and stop in unison, in contrast to patterns recorded

TABLE 2.—*Simultaneous Leads from Three Motor Units of the Right (Spastic) Rectus Femoris Muscle in Gentle Voluntary Contraction (Patient 12, Aug. 29, 1938)**

	Leads			
	Distal	Middle	Proximal	Comment
1	38	37	35	Onset of contraction
2	60	50	46	
3	56	51	43	
4	51	51	49	
5	51	48	45	
6	52	49	48	
7	53	48	47	
8	50	48	45	
9	51	45	43	
10	49	45	41	
11	55	47	43	
12	49	32	25	Relaxation
13	15	6	7	After discharge
14	4	1?	2?	
*	634	358	514	

* Fourteen seconds' run, covering one complete action, including the beginning and the end. Spikes were counted per second.

TABLE 3.—*Spike Frequencies per Second in Simultaneous Leads from Three Motor Units of a Spastic Rectus Femoris Muscle (Patient 20, July 27, 1938)**

	Leads			
	Proximal	Middle	Distal	Comment
1	41	43	43	Synchronous beginning
2	46	43	50	
3	42	33	32	Relaxation
4	23	24	26	Beginning
5	45	47	47	
6	41	30	39	Relaxation
7	38	38	39	Beginning
8	41	40	49	
9	42	34	47	
	359	332	372	

* Three successive short innervations, three seconds each.

previously from normal muscles under similar conditions. Amplitudes vary in the different leads. It has been pointed out [3a] that this is probably due to the more or less accidental distance of the recording electrode from the active fiber groups. For the same reason, absolute amplitudes mean little with this technic of recording. In all of these experiments, however, the gain was about twice as high as in the experiments on normal muscle; yet spikes were never quite as high. This is suggestive of a reduction in voltage of the impulses in voluntary innervation of spastic muscles. The frequencies seen in moderate effort varied between

a few and 60 discharges per second. The frequency of discharge during strong effort cannot be adequately studied by means of ink writers, the upper limit for which is about 90 per second.

An additional observation shown in the lower record (fig. 2 *B*) should be emphasized: During rest in relaxed muscle no signs of action potentials are traceable. Action potentials start synchronously with movement.

ACTION POTENTIALS OF REFLEXES AND CLONUS

In contrast to the weakness, slowness and stiffness of voluntary movement in spastic extremities, proprioceptive reflexes are as a rule brisk and often powerful, and there is a tendency toward clonic repetition in general proportionate to the degree of reflex hyperactivity. Another property of spastic reflexes is curiously little mentioned in the clinical literature,[6c] though it was observable in more than one-half the cases of spasticity seen in this department. This is the spreading of deep reflexes to neighboring muscle groups or to muscles on the other side of the body or at other levels.

The action potentials of tendon reflexes recorded in cases of spasticity have a number of features in common which distinguish them from those of normal reflexes. The spikes which they produce are usually as high as or higher than those of normal reflexes. The normal reflex recorded from a surface lead consists of a short single spike, with an occasional equally short small single after-discharge wave, and the whole process is usually over in eight milliseconds. The spastic reflex traced from the stimulated muscle by surface electrodes (fig. 3) hardly ever consists of a single spike alone. Even in the rare instances in which it does it has a number of smaller spikes as precursors and as after-discharges, which are brought out only by a high gain. As a rule the response consists of a number of high spikes in a regular or irregular pattern with after-discharges, and the whole process lasts from fifteen to sixty milliseconds or more. In several instances a rhythmic sequence of after-discharges consisting of groups of small spikes was traced, as in figure 3 *A*. The after-discharges here last well over two thirds of a second. They imitate a clonus (see page 9) except for their small size and the fact that no clonic movement was observed. The after-discharge in this instance at least did not involve more than a small part of the fibers, unless there was subtotal stimulation of all the fibers, which for a number of reasons seems unlikely. The reflexes in this instance were elicited by repeated tapping of the tendon at a fairly fast rate, and the observer did not notice the after-discharge until the film was developed. Incidentally, the second full reflex response coincided with the third burst of the after-discharge from the first response. The second reflex response was not apparently different from the first, and there was no perceptible influence of a refractory period of the cord.[6c]

In a number of instances in which spreading of reflexes was seen clinically, reflex impulses were also traced from far distant muscles, though the latter were not observed to move. The phenomenon was rather unpredictable in its distribution. Reflex impulses could usually be recorded on both sides at levels above

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6. Foerster, O., and Altenburger, H.: Zur Physiologie und Pathologie der Sehnen-und Knochenphänomene und der Dehnungsreflexe: (*a*) III. Die Sehnen- und Knochenphänomene beim Pyramidenbahnsyndrom, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:779, 1933; (*b*) IV. Die Dehnungs-und Annäherungsreflexe beim Pyramidenbahnsyndrom, ibid. **148**:665, 1933; (*c*) V. Die Reflexsynergien beim Pyramidenbahnsyndrom, ibid. **149**:409, 1934.

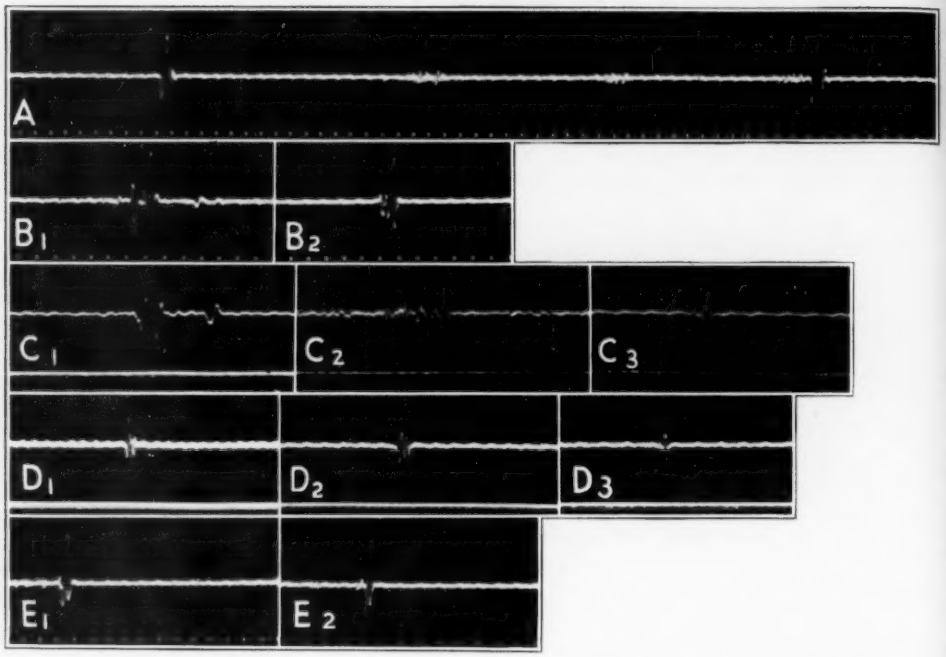

Fig. 3.—Spastic reflex action potentials in surface leads. Calibration and timing as indicated in figure 1. Cathode ray oscillograph.

A (patient 13, Feb. 1, 1938): Left ankle jerks; electrodes on musculature of left calf. Note irregular spike pattern. First response is followed by rhythmic "clonic" discharges; second reflex response immediately follows third group of after-discharges.

B 1 (patient 13, Feb. 1, 1938): Left knee jerk; electrodes on left quadriceps muscle. Note irregular spike pattern.

B 2 (patient 10, Dec. 23, 1937); Left ankle jerk; electrodes on musculature of left calf. Pattern of reflex is comparatively simple.

C and *D* (patient 6): Jan. 12, Feb. 5 and Feb. 16, 1937.

C 1: Right ankle jerk; electrodes on right calf.

C 2: Right knee jerk, spreading to and recorded from right calf.

C 3: Left knee jerk, spreading to and recorded from right calf. Spread is from normal to diseased side.

D 1: Left ankle jerk, recorded from left calf. Reflex on normal side has slightly "spastic" pattern.

D 2: Left knee jerk, spreading to and recorded from region of left calf. Spread is within "uninvolved" side.

D 3: Right knee jerk, spreading to and recorded from muscles of left calf. Spread is from hemiplegic to normal side.

Note in *C* and *D* the difference in patterns. All reflexes originating in a spastic muscle, except that shown in *D 3*, show a more complicated pattern than the reflexes originating in nonspastic muscles.

E (for comparison): Two normal ankle jerks. Note the slight variation.

and below the level at which the stimulus was given. This was not invariably the case, however, and when it occurred in one distant muscle it did not necessarily occur in others. With the exception of a questionable extensor thrust in 1 case, there was no obvious pattern, or *Gestalt*. Spreading of reflexes has never been observed in normal subjects or in patients without other evidence of disease of the pyramidal tract.

In cases of hemiplegia reflex irradiation was seen from the diseased to the normal side and vice versa. In 1 instance, that of a hemiplegic patient, reflexes spread within the otherwise relatively normal side.

The farther a reflex has spread from its place of origin the smaller is its potential and the less complicated its pattern. There is suggestive evidence to show that on the whole reflexes spreading from a normal muscle do so as single spikes, while reflexes originating in a spastic area are transmitted as "spastic" reflexes. A number of reflex patterns are seen in figure 3, in which examples of reflex irradiation are shown in the third and fourth series of records.

In a number of observations, simultaneous leads from proprioceptive reflexes were taken with coaxial needle electrodes in order to investigate the relation to one another of separate motor units in a single muscle. One series of homolateral and one of contralateral patellar reflexes are presented in figure 4. They were recorded from the right rectus femoris muscle of a patient who had suffered an injury of the cord at the cervical level and who showed paraparesis. The reflexes were elicited by tapping the patellar tendon repeatedly at a rate of about 1 per second, first on the right side, then on the left. In both series there is complete synchronicity of all three leads. Here, again, the direct reflex is of a more complex nature than the one spreading from the other side. Both show another characteristic of spastic reflexes in the variety of responses to apparently equal stimuli.

In several instances it was noted that reflexes spreading from a distant muscle, such as from the biceps to the musculature of the contralateral calf, did not appear with the first stimulation, but occurred after several attempts. Apparently, in certain cases at least, spreading of reflexes is facilitated by repeated stimuli.

The electromyographic pattern of clonus is much more uniform than that of single proprioceptive reflexes, and the single thrust differs in several respects from the single reflex. Electrically, a clonus appears as a sequence of rhythmic bursts at an average rate of about 6 per second, the frequency being fairly constant in many cases, increasing or decreasing to a certain extent in others but usually remaining in the same range in different tracings from the same patient. There is also a certain variation in the maximal amplitude of the bursts. The single burst consists of a group of spikes, usually, but not invariably, arranged in a "staircase" pattern, with the highest spike in the middle. In this respect and in the number of spikes, the individual burst of a clonus is different from the pattern of an ordinary tendon reflex. The number of spikes per burst varies from 9 to 19, with an average of 14. The average duration of the individual group of spikes is forty-four milliseconds, with a range of thirty-three to sixty-six milliseconds. The average rate is 6.4 per second, with a range of 5.6 to 7.4 per second. The rate of spikes per second would be 316 as an average, 280 being the lowest and 360 the highest figure extrapolated from the duration and number of spikes per burst. These data are derived from an analysis of 6 cases, taken at random.

Records taken from patellar clonus and those obtained from ankle clonus do not differ in any respect, nor is there a difference between clonuses elicited by the examiner and those occurring apparently spontaneously in "spinal epilepsy."

In a great number of instances clonuses were recorded with surface leads and with coaxial needle leads in successive runs with the cathode ray oscillograph. It was found that patterns, frequencies, number of spikes and other characteristics were so similar in both leads as to suggest a similar process, which means a tendency to synchronization of all the units active in one burst of clonus. Four examples of clonus are presented in figure 5. They are, from top to bottom: a record of ankle clonus in a surface lead (*A*), followed by a record from a coaxial lead on the same patient (*B*), while the third record (*C*), similar to the previous one, is again from a surface lead on a different patient. The last picture (*D*) is that of a spontaneous clonus, again in a surface lead. Here and in the second example of clonus, small bursts of activity, perhaps picked up from the antagonist, can be seen alternating with the large groups.

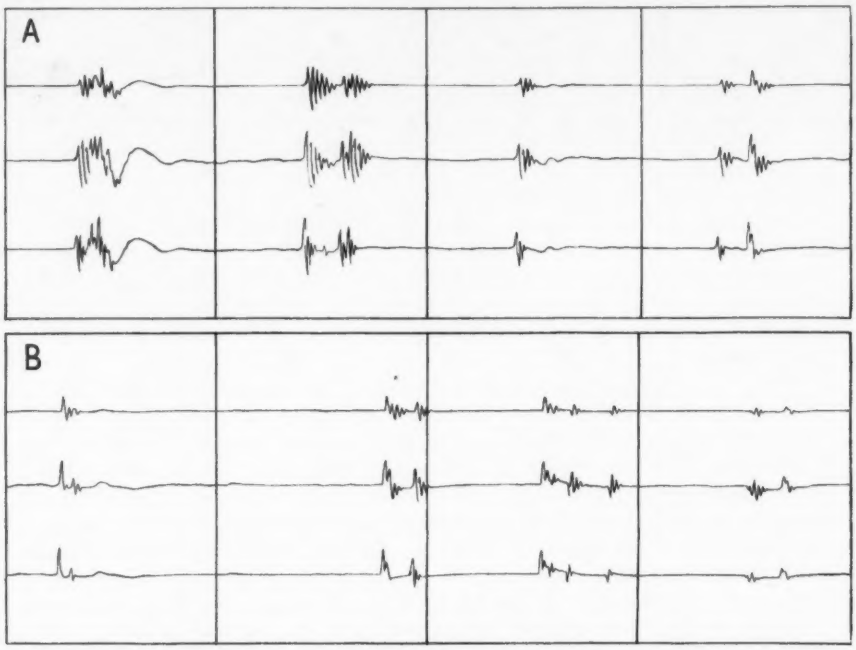

Fig. 4.—Spastic reflex action potentials in simultaneous coaxial electrode leads placed in the left rectus femoris muscle (patient 10, Sept. 1, 1938). Time: one second between vertical lines. Calibration: 6 mm. per hundred microvolts. Ink-writing oscillograph.

A: Left knee jerks elicited four times in succession.

B: Right knee jerks, elicited four times in succession, spreading to left side.

Note full synchronization in both series of reflexes and variety of responses and appreciably less complicated structure of spreading reflexes (lower series).

It has been pointed out before that the ink-writing oscillograph is too slow for accurate recording of high frequency phenomena such as the spikes of a clonus. It is possible, however, to trace the *groups* of bursts. Thus, in 2 instances of clonus simultaneous tracings were made from coaxial and surface leads. One of these attempts is presented in figure 6. It shows well the synchronization, and also the variation in amplitude of the single bursts in both kinds of leads.

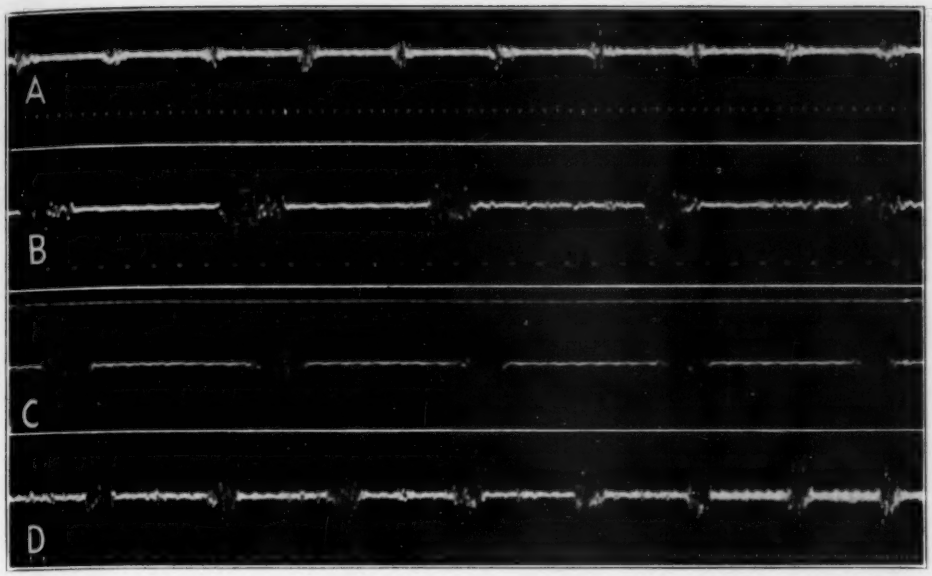

Fig. 5.—Clonuses in surface and coaxial needle leads. Time and calibration as indicated in figure 1. Cathode ray oscillograph.

A (patient 10, Dec. *22*, 1937): Left ankle clonus, surface lead. Note low speed of camera.

B (same observation, but with coaxial leads and camera at higher speed). Note small rhythmic bursts between large ones.

C (patient 7, Jan. 12, 1937): Left ankle clonus, surface lead. Note similarity to *B*.

D (patient 14, March 12, 1938): Spontaneous left ankle clonus, surface lead. Note small discharges between large groups, as in *B*. The "staircase" pattern is shown in all records; frequency and number of spikes are similar in "motor unit" (*B*) and in surface leads (*C* and *D*).

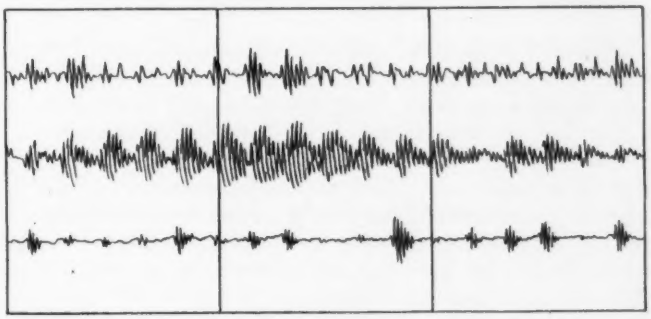

Fig. 6.—Simultaneous tracings from two coaxiai needle leads (two upper records) and a surface lead of ankle clonus on the right side (patient 16, Jan. 21, 1939). Ink-writing oscillograph. Time: one second between vertical lines. Calibration: about 6 mm. per hundred microvolts.

This record is not a true clonus tracing because the ink writers do not follow the spike frequencies characteristic of clonus. It is, however, possible to compare the whole bursts in the different leads. Amplitude of spikes means little with this recording technic. It is noteworthy, however, that in the same lead, best seen in the last record, intensities vary considerably.

ACTION POTENTIALS DURING SPONTANEOUS INVOLUNTARY ACTIVITY

Involuntary activity could be observed as fibrillary or coarser fascicular twitchings or, always incidentally, as tonic movements of smaller muscle fiber groups and as mass movements.

Fibrillary twitchings of a single motor unit have been described previously [3a] as examples of single spike activities. A group of fibrillating units is seen in the upper record of figure 7. They were led off with a pair of coaxial electrodes from the extensor muscle of the index finger of a patient suffering from amyotrophic lateral sclerosis. It had been previously noted that elicitation of the biceps jerk increased the fibrillations, and the electromyographic examination confirmed the observation, as figure 7 *B* shows. This seems to indicate not only that the biceps reflex irradiated to the neuron innervating the finger muscle, but also that the spreading reflex set up a long-lasting disturbance, presumably in the same group of anterior horn cells.

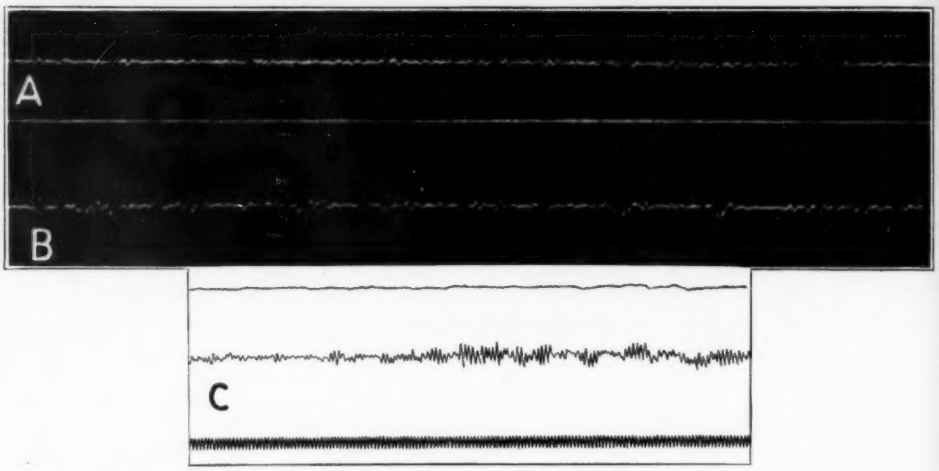

Fig. 7.—Spastic involuntary movement in coaxial needle leads. The two upper records were taken with a cathode ray oscillograph; the lower record was taken with the ink-writing oscillograph. Calibrations for both oscillographs as in the preceding figures. Time in lower record: a 60 cycle alternating current, recorded with ink writer.

A and *B* (patient 22, Jan. 21, 1939): Fibrillations of left extensor digitorum communis muscle (*A*) at normal rate and (*B*) at increase in rate and probably in number of units involved after elicitation of left biceps reflex.

C (patient 10, Jan. 20, 1938): "Tonic" innervation of fiber group observed incidentally in left quadriceps femoris muscle.

A "tonic" burst of spike potentials, recorded from a fiber bundle only, while the surface lead of the whole muscle showed no activity, is seen in the lowest record of figure 7.

Mass reflexes showed a similarity in pattern of motor unit and whole muscle potentials, in simultaneous leads, like that seen in other reflex and voluntary movement.

It should be emphasized once more (see fig. 2 *B*) that these action potentials are usually seen associated with movements. In a few instances no gross movement could be observed, as in those in which spikes were recorded only from a fiber bundle in the depth of the muscle. At no time was a constant, regular sequence of action potentials seen in a spastic muscle during rest, that is, when the muscle was not stimulated by voluntary effort, reflex actvity or the action of gravity on the limb.

ACTION POTENTIALS DURING PASSIVE MOVEMENT

A peculiar resistance to passive movement has given spasticity its name. It is experienced by the examiner as well as by the patient himself. In a number of cases action potentials were recorded of passive movements, carried out by the observer or by the patient himself, innervating voluntarily the antagonist of the muscle under observation.

Both types of experiments are presented in figure 8. The first three records were taken with surface electrodes from the calf musculature of a patient presenting spastic hemiplegia. Figure 8 *A* shows the muscle at complete rest, when no activity can be observed. The next record (fig. 8 *B*) shows the beginning of passive movement, in this instance a steady dorsal flexion of the foot carried out by the examiner, while the third record is the direct continuation of the second. The response begins at the last third of the second strip with a short group of small spikes, followed after about one tenth of a second by another group of even smaller potentials of longer duration and, finally, by a somewhat irregular clonic sequence of groups of after-discharges not accompanied by any movement.

Figure 8 *D* shows in its beginning a response to a brisk stretch, which at first failed to produce ankle clonus, though one begins later in a slightly irregular fashion. The patient was hemiplegic. The record was taken from the calf musculature by means of surface electrodes.

The last two records (fig. 8 *E* and *F*) show strips of a tracing with surface electrodes from the calf musculature in a third case of spastic hemiplegia. The patient was asked to lift his foot against moderate resistance. While, again, no activity is observable during rest, the effort of the patient, which amounted to passive stretching of the antagonist of the innervated muscle, produced a pattern of action potentials not very different from that seen in weak voluntary innervation. The amplitudes of the spikes are small; the frequency, somewhat irregular, is about 200 per second. The whole process lasts as long as the active movement by which it is produced.

INFLUENCE OF CURARE ON SPASTIC INNERVATION

Curare has been administered for the relief of a variety of nervous diseases since shortly after its action was recognized by Claude Bernard. Recently, West [7] and Burman [8] have reported benefit from its use. It has been employed in a number of instances during this investigation. Several different solutions were used by intravenous injection. It is not easy to establish the proper dose for a given

7. West, R.: Intravenous Curarine in the Treatment of Tetanus, Lancet **1**: 12, 1936; The Pharmacology and Therapeutics of Curare and Its Constituents, Proc. Roy. Soc. Med. (Sect. Therap. & Pharmacol.) **28**:41, 1935.

8. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**:307 (Feb.) 1939.

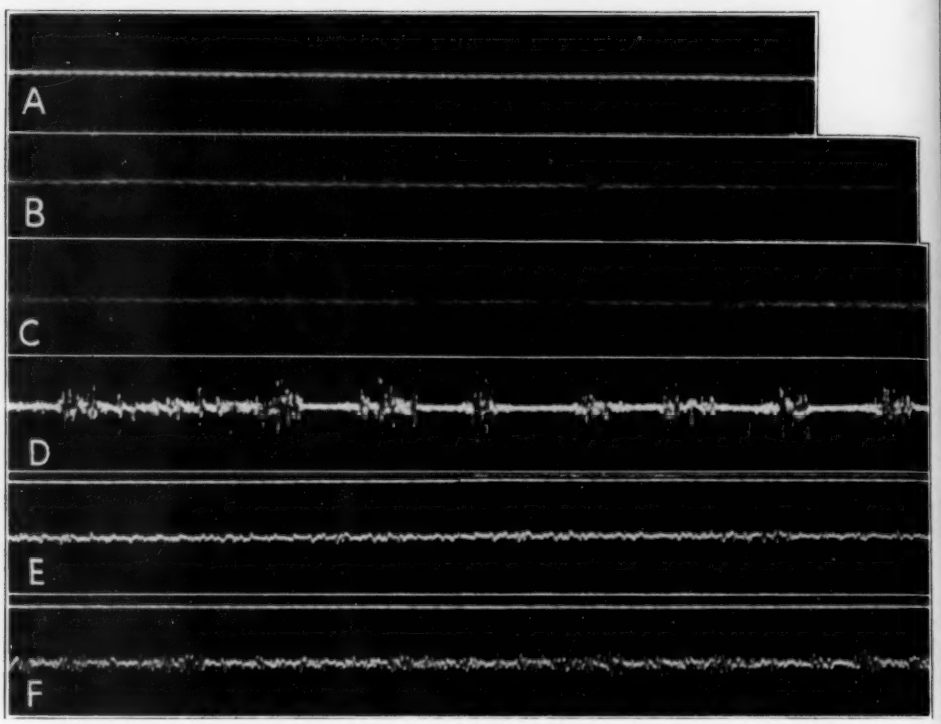

Fig. 8.—Spastic muscles at rest and in response to stretching. Surface leads. Cathode ray oscillograph. Calibration and timing as indicated in figure 1.

A to *C* (patient 25, May 2, 1939): Musculature of left calf. *A*, at rest; *B*, stretching by the examiner, beginning at about the last third of the record, and *C*, continuation of *B*. Note the slightly irregular pattern, suggestive of clonus.

D (patient 12): Musculature of the right calf; unsuccessful attempt to elicit ankle clonus during first third of record, followed by clonus eventually.

E and *F* (patient 6, Jan. 14, 1937): Musculature of left calf, stretched by voluntary contraction of tibialis anticus muscle. *E*, beginning of effort; *F*, height of effort.

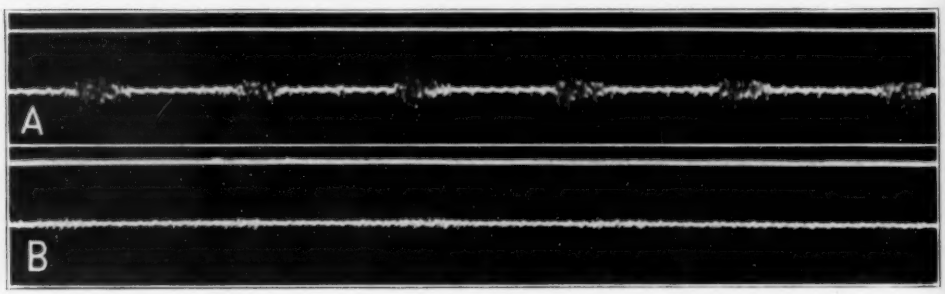

Fig. 9.—Effect of curare on ankle clonus in surface leads (patient 6, Feb. 5, 1937). Cathode ray oscillograph. Calibration and timing as indicated in figure 1. *A*, clonus before curare: *B*, electromyographic response to unsuccessful attempt to elicit clonus. Note small groups of bursts, maintaining old clonus rhythm.

patient. It was possible on several occasions to abolish ankle clonus in 1 patient for about a day at a time, during which period his spastic stiffness was greatly diminished. The clonus before injection of curare and what is visible in electromyograms after a successful administration of the drug are shown in figure 9 *A* and B. On close inspection of 9 *B*, small regular bursts are visible, resembling a clonus in rate and number of spikes. No clonic movement could be produced, however.

COMMENT

A survey of the electromyographic patterns obtained from muscles in spasticity has been given in this report. A number of clinical signs which belong to the spastic syndrome as it has been defined in the introductory paragraphs were studied.

Maximal voluntary innervation of spastic muscles is characterized by spike amplitudes which are considerably smaller than those seen in normal subjects.[3a] This difference tends to become less significant when the actual strength of the movements is compared. In most instances, for example in the hand grip, motor power is considerably diminished, and in antigravity muscles strong enough to enable a patient to walk the spike amplitudes are in the low normal range. Contractility does not appear to be actually impaired in spastic muscles, and the explanation for the weakness of effort in certain muscle groups has to be sought elsewhere. A less significant difference between normal and spastic movement lies in the frequencies of the spikes. They are lower in spastic muscles, again roughly in proportion to the strength of successful effort. A third, and again a slight, difference of spastic muscles from the normal is the unevenness of the rate and amplitude of spikes and their tendency toward grouping in the action potential sequences. No great abnormality is thus revealed by surface leads from spastic muscles.

The behavior of the antagonists during innervation of the protagonists will be dealt with later. It may be mentioned here that activity is seen in the antagonists identical with that seen in passive movement.

In simultaneous motor unit leads an essential contrast between the management of spastic and that of normal muscles is brought out. In normal subjects, records obtained from three pairs of coaxial electrodes placed in one muscle showed complete independence of each other.[3a] There was little or no relation of the single units in respect to frequencies, patterns and, indeed, activity or inactivity of one or the other leads, so that even during increasing activity of the whole muscle one unit might stop discharging for a while. It appears that this alternation of activity enables muscular contraction to be sustained with a minimum of fatigue. Under identical conditions motor units of a spastic muscle show a strong tendency to synchronization in frequency and pattern, which can safely be regarded as a characteristic of the pathologic state. This is true both of the muscles chiefly involved, as the flexors

of the arm and the extensors of the leg, and of their antagonists. With the technic employed, spike amplitudes have been consistently lower than in normal muscles, while the frequency range, for moderate effort, has been about the same as in normal muscles. Again, as in normal subjects, it has been impossible for technical reasons to establish the upper limit of frequency for the individual motor unit.

It was difficult to interpret the difference in the voltage of discharges in normal muscles, namely, the "staircase" pattern alternating with stretches of regular discharges of identical size.[3a] Other apparent contradictions to the "all or none" law were also observed, which await explanation.

At this stage of the investigation it is not essential to attribute the patterns observed to a single unit alone. The important fact is that two types of management of muscle can be established.

Reflexes and clonuses show the same synchronization of motor units as do voluntary movements. This holds true for all details of the patterns of both homolateral and contralateral spreading reflexes.

Normal proprioceptive reflexes are similarly synchronized. In maximal as well as in submaximal responses all the active fibers discharge at the same time, and correspondingly large or small spikes are recorded.[3a]

The chief characteristics of spastic reflexes are: (1) complexity of pattern, (2) a tendency to after-discharge and (3) a tendency to spreading to other muscles. In addition, in reflexes elicited in quick succession a variation of responses to apparently equal stimuli may be seen in 1 patient.

There are several conceivable explanations for the repetition of spikes in irregular pattern, possibly also for the after-discharges, which usually consist of small spikes closely following the large ones. It might be assumed, for example, that the conduction in certain parts of the fibers of the lower neuron or in the neuromuscular synapse is delayed, so that impulses leaving the anterior horn cells at the same time arrive at the muscle at different times. This explanation is hardly satisfactory, as there is no reason to assume a change in conduction along the neuron. Furthermore, the fact that all the active parts of the muscle show the same pattern in coaxial needle leads as appears in leads from the whole muscle disproves this assumption.

It must be concluded, therefore, that the action potential group traced from the muscle originates either in the afferent fibers arising from the muscle or in peripheral motor neurons. Anatomically, the sensory fibers are intact, and there seems no more reason to hold them responsible for the electrical phenomena in spastic than in normal muscles.

A standard explanation for the phenomena of spasticity is the theory of "release" of spinal mechanisms as a result of anatomic or physio-

logic interruption, complete or partial, of the corticospinal motor system. It has been assumed that the presence of the intact corticospinal system exerts an inhibitory influence on the segmental functions of the cord, leaving them just enough independence to manage posture and carry out similar tasks.

The spastic reflex pattern may be related to the spreading of reflexes. Volleys of impulses arriving simultaneously from all the activated centripetal fibers at one or two segments of the cord arouse a reflex activity (most likely excessive) which spreads into collateral intraspinal systems. Reflexes, split up in this fashion, may thus reach their final destination by way of one or several "delaying pathways,"[9] in addition to the regular short connection, and spike potentials will arrive therefore at the muscle at different times and with varying intensities left. This conception would explain the variation in amplitude of spike potentials, which is typical of the spastic reflex pattern, and might also explain the variable, but usually increased, strength of the reflex jerk. Other impulses run completely astray and become liminal or subliminal stimuli for distant muscles. Accordingly, they become manifest as "spreading" reflexes or are detected by high amplification as spreading "escaped" impulses in the muscles. This hypothesis might explain also the long-lasting increase of fibrillations occasionally set up by reflexes at a distance of several segments. Such a disturbance may last for the better part of a second and involves probably another local mechanism. Forbes[9] has shown that a motor neuron may discharge repeatedly in response to a single afferent excitation, and it might be supposed to do so with any excitation. Furthermore, it was shown by Forbes and his associates[10] and by one of us (P. H.)[3b] that a synapse, like the neuromyic junction, may "store" excitations, such as repeated electrical stimuli, and set up impulses with increasing delay over a period much longer than the interval between the first and the last stimulus.

It is suggested that all these phenomena are different aspects of one "old" mechanism,[11] revealed by the absence of corticospinal control.

The spread of reflexes from the relatively normal to the diseased side and even within the uninvolved side in cases of hemiplegia is comprehensible in view of the results of experiments by Hoff and Hoff,[12] who

9. Forbes, A.: The Interpretation of Spinal Reflexes in Forms of Present Knowledge of Nerve Conduction, Physiol. Rev. **2**:361, 1922.

10. Forbes, A.; Ray, L. H., and Griffith, F. R.: The Nature of the Delay in the Response to the Second of Two Stimuli in Nerve and in the Nerve-Muscle Preparation, Am. J. Physiol. **66**:553, 1923.

11. Wilson, K. S. A.: The Old Motor System and the New, in Modern Problems in Neurology, London, Edward Arnold & Co., 1928, chap. 6.

12. Hoff, E. C., and Hoff, H. E.: Spinal Terminations of the Projection Fibers from the Motor Cortex of Primates, Brain **57**:454, 1934.

showed that after unilateral ablations of motor and premotor areas terminal endings of the corticospinal projection fibers degenerate on both sides of the cord to a varying degree. Thus, a slight release might be expected even on the nonparalyzed side.

The electromyographic pattern of clonus as it was traced in these observations is well in accord with the findings of earlier investigators.[13] Clonus and clonic after-discharge are not easy to understand because, in spite of their close relationship to reflexes, they show a great regularity in pattern and rhythm. They also consist individually of a large number of spikes at frequencies up to 360 per second. As clonus is an alternating innervation of protagonist and antagonist kept up by itself, it is likely that a larger number of cells is active, covering perhaps the entire area for both groups of muscles in the cord. This should probably be regarded as a center with regulating properties, not simply as a network within which impulses irradiate irregularly wherever a pathway happens to be open. Impulses from a clonus were never detected in other reflex arcs, though repeated attempts were made to find such an irradiation.

The clonic after-discharge following a spastic tendon reflex, as shown in figure 3 *A*, and also the residual clonic pattern seen after abolition of the clonic movements by curare are interesting in several respects. The small amplitude of the spikes and the fact that no rhythmic movement was observed in either instance seem to indicate that only few of the fibers are involved in these phenomena. The configuration in both instances is, however, similar to that of a true clonus, and the conclusion seems justified that the synchronizing mechanism is active as before, even if only a small number of fibers is involved.

A rough attempt was made in several instances to measure the approximate motor power of clonus. The foot of a patient was placed on a small platform scale. With the subject at rest, a certain deflection due to the weight of the foot and lower part of the leg occurred, and its extent was noted. When the clonus was elicited an additional rhythmic deflection, of a range of from 2 to 4 Kg., was observed. The energy involved, therefore, is small as compared with that developed in voluntary innervation. The spike frequency is, however, as high as that in maximal voluntary effort.

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13. (*a*) Gregor, A., and Schilder, P.: Zur Methodik der Untersuchung der Muskelinnervation mit dem Saitengalvanometer, Ztschr. f. d. ges. Neurol. u. Psychiat. **15**:604, 1913. (*b*) Bornstein, A., and Saenger, A.: Untersuchungen über den Tremor und andere pathologische Bewegungsformen mit dem Saitengalvanometer, Deutsche Ztschr. f. Nervenh. **52**:1, 1914. (*c*) Cobb, S.: Electrographic Studies of Clonus, Bull. Johns Hopkins Hosp. **29**:247, 1918. (*d*) Foerster and Altenburger.[6] (*e*) Lindsley, D. B.: Electromyographic Studies of Neuromuscular Disorders, Arch. Neurol. & Psychiat. **36**:128 (July) 1936.

Of great interest, again, is the synchronous discharge of motor units in clonus. It seems clear that motor units are able to carry as many as 360 impulses per second, irrespective of the number of synchronized units assumed to be picked up by the coaxial electrodes. In normal voluntary innervation the upper range safely attributable to one unit has been about 125 per second.

Foerster and Altenburger [6c] showed that the rate of discharge in clonus does not indicate the refractory period of the spinal cord, as previous authors had stated. This they demonstrated by eliciting tendon jerks between bursts of clonus. They were the first to recognize the reflex nature of the action potentials occurring in passive stretching of spastic muscle.

No action potentials were found in resting spastic muscles. It is therefore concluded that there is no "tonic" spastic innervation and that spasticity is produced as a reflex by passive motion carried out by the examiner or by the patient himself or by gravity. The muscles involved by hemiplegia are not in spasm when at rest, but are weak, to a degree which varies for different muscle groups, and this circumstance causes a certain fixation through preponderance of one muscle group over another, for example, of the flexors over the extensors in the arms.

Innervation of antagonists during voluntary or involuntary movement in any spastic group of muscles has thus to be regarded as a reflex phenomenon. There is no reason to assume a simultaneous innervation of protagonists and antagonists from higher centers, as in certain types of involuntary movements.[14]

It has been impossible to confirm the observations made by Gregor and Schilder,[13a] by Bornstein and Saenger [13b] and, more recently, by Lindsley,[13c] who all found a continuous presence of action potentials throughout the spastic muscles during rest. Whenever potentials were seen they were referable to direct or reflex motion.

It is easy to overlook such a relation of action potentials to actual motion, especially if only a few patients are studied and if not all clinical features of a given case are considered.

Fibrillary or fascicular twitches may be mistaken for impulses maintaining a spastic tonus, postulated by a number of older authors. They may be expected in any muscle undergoing atrophy, even to a subclinical degree, in addition to being subject to spasticity. They have been known to occur not only in cases of lesion of the spinal cord but also in certain cases of cortical hemiplegia.

On the other hand, it is necessary to take the low reflex threshold into consideration. Tension in a muscle due to gravity or to a constrained

14. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Athetosis and Chorea, Arch. Neurol. & Psychiat., to be published.

posture is a sufficient stimulus to produce reflex responses, both in the muscle under strain and in its antagonist.

In a large number of repeated observations with high amplification, no sign of electrical activity was found when proper precautions were taken.

Curare was found to depress clonus completely in a few instances, although traces of clonic bursts were still perceptible in the electromyogram. In another group of experiments [15] it was observed that the motor strength and also the frequency in electromyograms of a voluntary effort were unchanged by a dose of curare sufficient to abolish a parkinsonian tremor. Bremer and Titeca,[16] in a study of the influence of this drug on decerebrate rigidity, concluded that impulses of a certain range of frequency are blocked by curare, while slow impulses still pass the neuromyic junction. They interpreted the effect of curare as a Wedensky inhibition. No specific influence of curare on certain frequency ranges could be observed in our own experiments, since voluntary innervation and clonus, as well as tremor, show frequencies from about 300 to 350 a second. It is probable, therefore, that curare may exert a central, as well as a peripheral, action. One of us [17] reached the same conclusion after observing that nerve impulses in response to acid stimulation of the skin in "reflex" frogs may disappear after curarization.

In conclusion, an attempt may be made to understand the management of muscles in spastic conditions. In accord with the findings discussed here, the assumption seems justified that older motor systems of the spinal cord [11] come into action after abolition of part or all of the control of the corticospinal systems. Spasticity is subserved by an intrinsic system, since certain phenomena, such as exaggerated, spreading reflexes, clonuses and the synchronization of motor units, are seen in the muscles of patients with transverse lesions of the spinal cord after presumable degeneration of all exogenous descending fibers, as well as in cases of cortical or capsular hemiplegias.

Two characteristics of the method of operation of the released intrinsic mechanism of the spinal cord are particularly striking: the widespread and long-lasting nature of the reflexes and the tendency to synchronization of motor units.

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15. Hoefer, P. F. A., and Putnam, T. J.: (*a*) Electromyographic Studies in Spastic Conditions and in Paralysis Agitans, Arch. Neurol. & Psychiat. **40**:1050 (Nov.) 1938; (*b*) Action Potentials of Muscles in Rigidity and Tremor, ibid., to be published.

16. Bremer, F., and Titeca, J.: Atonie curarique et inhibition de Wedensky, Arch. internat. de physiol. **42**:223, 1935.

17. Hoefer, P. F. A.: Versuche über Nervenaktionsströme: IV. Ueber die elektrischen Vorgänge bei spontaner, bei sensibler und bei reflektorischer Erregung, Ztschr. f. Biol. **95**:64, 1934.

In cases of incomplete interruption of the corticospinal tracts, i. e., in the instances in which a certain amount of voluntary control is left, the question arises how the remnants of volitional movement are managed. It has been suggested that undifferentiated "mass movements," for instance, of a hand when a finger movement alone is intended, are produced by "premotor" centers of the cortex and by their connections the "extrapyramidal" systems.[2] Considering, however, the identity of pattern of muscle management seen after both lesions of the spinal cord and those of the corticospinal tracts above the midbrain, it seems reasonable to assume instead that in both instances the intrinsic primitive and synchronized motor system of the cord is the main source of motor innervation, and that it may be set in motion by even small remnants of the corticospinal and perhaps other long tracts. Thus, in addition to cortical impulses, the basal ganglia also may conceivably exert an influence on the intrinsic system of the cord through "tonic" innervation or by impressing other patterns of movement on it. In this manner, certain movements may occur partly "at will," and the presence of these movements and their extent constitute the difference between the spastic hemiplegic patient and the "spinal" man.

SUMMARY

Action potentials of muscles in patients presenting spastic conditions have been studied. A number of features apparently characteristic of spastic innervation have been described.

1. Voluntary innervation, whenever it is possible at all, is found to be weak both by ordinary observation and in terms of frequency and amplitude of the spike potentials produced. The management of innervation is revealed by comparison of motor unit and surface leads. Simultaneous motor unit leads show more or less complete synchronization in all muscles examined. This synchronization is considered a specific mechanism characteristic of the management of muscles in spasticity.

2. Spastic reflexes show a complicated pattern of tall spikes with after-discharges of irregular or occasionally regular grouping. They usually irradiate to muscles served by other reflex arcs at other levels of the cord and may reach the other side of the body. This behavior may be explained by a spreading of impulses in the intrinsic fiber systems of the cord. An impulse may be conducted over several "delaying pathways" and thus produce a repetition of spikes in a muscle whenever a "delayed" impulse returns. It may, on the other hand, run astray and reach other levels. Such an impulse may set up a long-lasting disturbance in a distant group of anterior horn cells, as in a case of amyotrophic

lateral sclerosis. Both "direct" and irradiating reflexes produce synchronization of all activated units.

3. Clonus produces synchronization of motor units, as simultaneous and successive leads from whole muscles and pairs of coaxial electrodes show. The pattern of clonus is regular, indicating that in clonus a temporary center is formed by which the alternating innervation of protagonist and antagonist is sustained.

4. No "spastic" innervation of a resting muscle was observed, and it is concluded that spastic "tonus" does not exist except as a reflex innervation, facilitated by the general hyperirritability. Spastic resistance is therefore probably to be considered a reflex phenomenon produced by stretching of a muscle either by the examiner or by the patient himself, when he tries to innervate an antagonist of the muscle in which spasticity is perceived.

5. Curare can be used to reduce spasticity. There are two possible sites of action: either on the neuromyic junction or on centers presumably in the cord. Curare does not appear to act by way of a Wedensky inhibition in spastic patients. With proper doses volitional innervation is not appreciably disturbed.

6. Management of muscles in spasticity is explained by the release of activity of the "old" motor system of the cord by total or partial loss of the corticospinal control. Synchronization of motor units and increase in reflexes are characteristic features of this mode of innervation. In case of subtotal loss of corticospinal control the remnants of the corticospinal systems suffice to set off the intrinsic system. Voluntary movement can thus be performed to a certain extent. This explanation of undifferentiated "mass movement" is preferred to the one by which it is related to circumscribed lesions of cortical areas.

RESULTS OF EXPERIMENTAL REMOVAL OF PINEAL GLAND IN YOUNG MAMMALS

LOYAL DAVIS, M.D.
AND
JOHN MARTIN, M.D.
CHICAGO

Since the beginning of the present century there has existed a quiet but continuous dissension among neurophysiologists on the question of the significance of the epiphysis. Indeed, the argument goes back much further, for in 1576 Galen [1] described the "conarium" and called it a gland; Descartes,[2] in 1649, conceived the structure to be the "seat of the soul"; Majendie,[3] in 1795, with more practical application, expressed the belief that the pineal body played a mechanical role in the flow of the cerebrospinal fluid. Since then, many investigators have studied the epiphysis and assigned to it various roles: a stimulator of sexual growth; an inhibitor of sexual growth; a rudimentary third eye carried over from the reptile stage; a true endocrine gland; a nonglandular structure with regressive characteristits as the phyla ascend, and a structure with no function of any nature whatever.

Regardless of its degree or nature of action as a glandular structure, the epiphysis may with all certainty and propriety be called a gland, the pineal gland. There is too much experimental and histologic evidence now available to deny this conception of its anatomic classification. That it is rudimentary and without morphologic evidence of glandular structure is still held by some, in the face of proof to the contrary; that it is a degenerate representative of the third eye of the Lacertidae is without actual substantiation in mammals; that it possesses spiritual power is hardly tenable in the twentieth century, but that it is a gland, possibly with definite physiologic action related to the endocrine system of the body, is held to be likely or true by an increasingly large number of investigators who have gleaned sufficient experimental and clinical data to support such a premise. There is a large volume of unbiased evidence available at this time which indicates that the pineal gland has a direct relationship to the process of

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From the Division of Surgery, Northwestern University Medical School.

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1. Galen: De usu partium, in Galeni omnia quae exstant opera, ed. 7, Venetiis, 1576, vol. 1, bk. 8, chap. 3.

2. Descartes, R.: Les passions de l'ame, Amsterdam, 1649, articles 31 and 32.

3. Majendie, F.: Encefalotomia di alcuni Quadrupi, 1795, vol. 4, p. 31.

somatic and sexual maturation, and that eventually it may be classified in hormonic relation to the hypophysis, gonads, adrenals and thyroid.

In many instances the published reports concerning the developmental and physiologic significance of the pineal gland are a source of but little satisfaction. These reports cover three general fields: (1) an attempt at a physiologic interpretation of the symptoms of patients with tumors of the pineal gland; (2) phylogenetic and embryologic investigations which, by tracing the history of the organ and by careful histologic study, would elucidate by inference the functional significance of the pineal gland; (3) investigations, concerned with various animals, in which the physiology of the pineal gland has been studied by extirpation and by the administration of glandular extract or substance. In the past few years some investigators, mainly European, have attempted to put the glandular extracts to a therapeutic use in human subjects.

Many series of cases of pubertas praecox associated with pinealomas have been reported, and it is this syndrome, more than any other one clinical entity, which has given support to the theory that the pineal gland in early life acts in some manner to regulate sexual and somatic growth. In most of these cases premature sexual development has occurred in males, as was pointed out in 1916 by Horrax,[4] although in a few it has occurred in females. It must be pointed out, however, that many cases of pinealomas have been observed in which there was no significant alteration in the secondary sexual characteristics of the patients. Whether the resultant sexual changes in patients with pinealomas are due to a specific tumor type, to the particular age of onset (even prenatal), to transmitted pressure effects to other portions of the midbrain, hypothalamus and hypophysis or merely to lack of normal pineal secretion, if there is such a secretion, has never been conclusively shown. Globus and Silbert,[5] in a presentation of a series of 7 tumors of the pineal region, established such tumors as true autochthonous teratomas, but the alterations in secondary sexual characteristics were not considered essential for the diagnosis of pinealomas. They expressed the belief that the cellular organization of the pineal body at an early stage of development points to its glandular character and justifies the term pineal "gland." They noted that at the age of about 5½ years the pineal gland approximates the mature state, and that thereafter the changes are mainly of a regressive nature, such as cyst formation, deposition of calcium, hyalinization and fibrosis. Haldeman[6] reviewed a large series of reported cases of pinealomas;

4. Horrax, G.: Studies on the Pineal Gland: II. Clinical Observations, Arch. Int. Med. **17**:627-645 (May) 1916.

5. Globus, J. H., and Silbert, S.: Pinealomas, Arch. Neurol. & Psychiat. **25**: 937-985 (May) 1931.

6. Haldeman, K. O.: Tumors of the Pineal Gland, Arch. Neurol. & Psychiat. **18**:724-754 (Nov.) 1927.

the large majority of the patients did not show altered sexual characteristics, but those who did show the syndrome of macrogenitosomia praecox were all boys between the ages of 3 and 16 years.

For scientific method and completeness of study no investigator has equaled Tilney in his researches on the significance of the pineal gland. Together with Warren,[7] he covered the phylogenetic development of the gland, studied it exhaustively from the histologic viewpoint, digested the pertinent clinical and experimental data and unequivocally labeled it a glandular structure with the capabilities of glandular function. He regarded it as a member of the endocrine system, admitting that the way in which its influence works is still obscure. Hortega [8] added the support of his detailed microscopic investigations of the organ in confirming it as a glandular structure with a specific, individual cell type capable of secretion. Bailey,[9] also on histologic grounds, refuted the claim of the structure to glandular properties. Krabbe,[10] in 1923, argued that the structure is truly a gland, and not a rudimentary leftover, and pointed out that, in addition to the fact that the structure of the pineal body is suggestive of a secretory function, a secretory activity has not yet been definitely disproved. He emphasized that the gland arises from the ependyma, that its histologic appearance simulates in some respects that of the other endocrine glands, that in early life it is highly vascular and that its cells show numerous amitoses.

Feeding experiments on animals [11] have in general led only to contradictory and inconstant results. Transplantation experiments [12] have

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7. Tilney, F.: The Pineal Gland, in Cowdry, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 10. Tilney, F., and Warren, L. F.: A Contribution to the Study of the Epiphysis Cerebri with an Interpretation of the Morphological, Physiological, and Clinical Evidence, American Anatomical Memoir, Philadelphia, Wistar Institute of Anatomy and Biology, 1919.

8. del Rio Hortega, P.: The Pineal Gland, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2.

9. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

10. Krabbe, K. H.: The Pineal Gland Especially in Relation to the Problem of Its Supposed Significance in Sexual Development, Endocrinology **7**:379-414, 1923.

11. (*a*) McCord, C. P.: The Pineal Gland in Relation to Somatic, Sexual, and Mental Development, J. A. M. A. **63**:232-235 (July 18) 1914. (*b*) Horrax, G.: Studies on the Pineal Gland: I. Experimental Observations, Arch. Int. Med. **17**: 607-626 (May) 1917. (*c*) Rowntree, L. G.; Clark, J. H.; Steinberg, A.; Hanson, A. M.; Einhorn, N. H., and Shannon, W. A.: Further Studies on the Thymus and Pineal Glands, Ann. Int. Med. **9**:359-375, 1935.

12. Dubowik, J. A.: Versuch einer hormonalen Beschleunigung des Wachstums junger Tiere, Endokrinologie **11**:15-22, 1932. Kozelka, A. W.: Implantation of Pineal Glands in the Leghorn Fowl, Proc. Soc. Exper. Biol. & Med. **30**:842-844, 1933.

likewise often resulted in confusing data. The most direct and conclusive results have been seen after extirpation of the pineal gland in young fowls and mammals, but here, too, there has been a wide divergence of opinion.[13] Some investigators[14] observed increased somatic and sexual growth following pinealectomy in young animals; others found no changes whatever;[15] but extirpation has not been shown to cause delayed or defective somatic or sexual maturation. A review of the numerous reports and the results stated therein would here be redundant. It must be noted, however, that many factors may influence the results of such investigations, among which may be named the complete or incomplete removal of the gland, the age at which the extirpation is done, the laboratory conditions affecting the normal development of the animals, the careful and intelligent use of controls, the traumatic effects of the operation, the side effects which may be produced by the feeding or injection of pineal substance or extract and the influence of heredity, with the factor of pedigreed and mongrel stock.

Goddard,[16] in 1917, used pineal extracts in backward children, without evidence of clinical change in his patients. More recently Aronstam,[17] citing Ratkowsky and Cingula, stated that increased libido and potentia have been produced in normal men by the administration of pineal substance. Engel[18] demonstrated the antigonadotropic character of a specific hormone of the pineal gland. He showed that the pineal body produces a substance which may increase or enhance the effect of the anterior lobe of the hypophysis. Increasing accounts of the therapeutic use of pineal extracts are appearing; many are interesting and arresting; many are obviously not well confirmed; few are convincing. But the fact remains that the trend of present day investigations does indicate the glandular character of the pineal body and the probability

13. (*a*) Dandy, W. E.: Extirpation of the Pineal Body, J. Exper. Med. **22**: 237-247, 1915. (*b*) Badertscher, J. A.: Results Following the Extirpation of the Pineal Gland in Newly Hatched Chicks, Anat. Rec. **28**:177-197, 1924. (*c*) Izawa, Y.: On Some Anatomical Changes Which Follow Removal of the Pineal Body from Both Sexes of the Immature Albino Rat, Am. J. Physiol. **77**:126-139, 1926. (*d*) Anderson, D. H., and Wolf, A.: Pinealectomy in Rats, with a Critical Survey of the Literature, J. Physiol. **81**:49-62, 1934. (*e*) D'Amour, M. C., and D'Amour, F. E.: Effects of Pinealectomy Over Several Generations, Proc. Soc. Exper. Biol. & Med. **37**:244-246, 1937. (*f*) Horrax.[11b]

14. Horrax.[11b] Izawa.[13c]

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of its rightful place on the register of endocrine organs. With all this, however, knowledge concerning the function and nature of the epiphysis is admittedly still in an unsatisfactory, obscure state, and the moment of complete elucidation does not seem imminent.

The purpose of the present investigation, concerned only with mammals, is to contribute additional information relative to the nature of the physiologic function of the pineal gland. An attempt has been made to reveal what, if any, its relationship may be to other glands of internal secretion; whether its action is one of stimulation or depression of somatic and sexual maturation; what effect on the animal's behavior its extirpation early in life may cause; what its effect on the reproductive cycle may be, and whether there are any notable variations from the normal in successive generations of pinealectomized animals. Enough data of a consistent nature have been accumulated to allow a suggestion of the probable action of the pineal gland in certain species, and to act as an incentive to further investigations carried out by the same as well as other methods. Thus far, all observations have been made on the results of extirpation of the pineal gland in the early phase of life in rats, cats and dogs, as soon as such a procedure was compatible with survival of the subject. The same studies are now in progress with Macacus rhesus monkeys.

This problem has been in progress for three and a half years. Standard laboratory conditions have been maintained; all animals have been operated on and reared under the same conditions, and standardized methods of study of the living animals as well as of the organs after autopsy have been followed. Any problem having to do with the rearing of young animals in a laboratory is necessarily fraught with many trials and disappointments. Because of our realization of this through experience, as well as our recognition of the disagreements now existing among physiologists and anatomists on the significance of the pineal gland, these investigations are being continued.

RATS

White rats producing litters of fairly uniform size, after uniform gestation periods, and maturing at a uniform age, were used in these experiments. Owing to the usual large size of the litters, it was possible in most cases to have controls, controls with operation on the skull and pinealectomized animals of both sexes in a single litter. On the eighteenth day after birth the rats were classified as to sex, and the ears were marked for permanent identification. The weight in grams and the length in centimeters from the external occipital protuberance to the tip of the tail were then recorded for each animal. With the animal under light ether anesthesia, the fuzzlike hair of the head was sponged with alcohol, and an incision, 1 cm. in length, was made through the skin in the midline over the vertex. With fine-pointed scissors a piece of bone, approximately 5 mm. square, was carefully removed near the midline over the left occipital area of the cerebrum.

Very fine forceps were then passed just under the confluens of the lateral and sagittal sinuses, where the pineal gland lies near the surface and in the apex of the crevice separating the two cerebral hemispheres, and the gland was carefully removed. When removal was successful it was done on the first attempt, and the gland could be positively identified. The hemorrhage, which usually occurred, was controlled by small moist cotton pledgets, and the scalp was then closed by two fine white silk sutures. On recovering consciousness in two or three minutes the animals were able to nurse. In 7 per cent of the animals death occurred within one-half hour, from hemorrhage. In one set of controls only the small piece of bone was removed. There was, of course, always in each litter a control animal of each sex which was not operated on. The postoperative course was invariably uneventful, without a single instance of infection. Weekly weights and measurements were made, and autopsies were performed on the animals at 90 days of age, when they had reached sexual maturity.

To date, eleven litters of rats have been studied, of which a total of 67 animals survived the operation, 24 being males and 43 females. Ten of this number subsequently either died before autopsy or were found at autopsy not to be completely pinealectomized, so that they have not been included in the final estimation of results.

After operation, the rats were left in the cage with the mother for approximately one month. During this period they nursed normally, learned to eat mash and drink from the water fountain and otherwise showed behavior which could only be called usual for young rats. No animals of either sex showed outward signs of sexual activity at the time of autopsy. A brief summary of the weights and measurements at autopsy may be seen in table 1. Three control females with operation on the skull grew much faster from the beginning of the experiment than did their litter mates, and their weights account for the increase in weight of this group of control females over either the females which were not operated on or the pinealectomized females. At 90 days of age, the time of autopsy, it was noted that there was no significant difference between the weights and lengths of the female rats which were not operated on and those of the pinealectomized female rats. This was likewise true of the males so far as lengths were concerned. However, there was a definite, though not large, increase in the weights of the pinealectomized males; judging from the gross appearance of the animals at autopsy, this weight was due to an increase of fat in the abdominal wall and around the viscera.

As can be seen in the table, there were no marked differences in the weights of the testes in any of the males. Three pinealectomized rats had testes and penis obviously larger than the average for the entire series, but this gross difference in the pinealectomized males was not a constant finding. Microscopically, the testes showed tubules with from four to five layers of cells, a few spermatozoa in the narrow lumens and, altogether, signs of only early function. There was no consistent

indication of an advance in maturity of the pinealectomized over the control males.

In well over half of the pinealectomized females the ovaries, on gross examination, appeared larger and more vascular than those of their controls. There was also in these animals an increase in the diameter, length and vascularity of the uteri and tubes. In 2 lesion females the external genitalia were of adult proportions at the time of autopsy. In the pinealectomized females which did not show this increase in size of the genitalia, the ovaries and uteri appeared approximately the same as those of the controls. Microscopically, every ovary, whether of a control or a lesion animal, showed that puberty was past; in fact, judging by the gonads, maturity was more apparent in the females than in the males. A wide variation was found in the number and size of the ripening

TABLE 1.—*Summary of Measurements on Rats*

	Weight, Gm.	Length, Cm.
Females		
Normal controls	96.9	26.6
Controls with operation on skull	102.4	26.7
Lesion animals	96.7	25.8
Males		
Normal controls	97.9	26.2
Controls with operation on skull	102.6	26.5
Lesion animals	105.8	26.6
Average weights of the two fresh testes		
Normal controls	1.57	
Controls with operation on skull	1.63	
Lesion animals	1.61	

ova, atretic follicles and atretic corpora lutea. The uteri and ovaries which were larger grossly showed microscopically a larger, more complex, more vascular organ than those in the remainder of the rats; likewise, a higher, richer villus formation was noted in the tubes of these females.

CATS

In the investigations made on cats, except in 1 instance, the stock was of the ordinary unpedigreed variety. In 1 experiment the kittens were thoroughbred blue Persians, and in the anticipation of possible criticism of the use of unpedigreed animals, more litters of thoroughbred stock will be used. All but a few of the animals were born outside the laboratory, being brought in at from 3 to 6 weeks of age. In no instance were the kittens allowed to be with the mothers after operation, thereby assuring uniform feeding standards. Owing to the small size of the litters, only normal controls of each sex were used, except in two litters which were large enough to permit the use of controls with operation on the skull.

When ready for operation, at about 6 weeks of age, the kittens were numbered and classified according to sex and litter. They were weighed and measured from the external occipital protuberance to the base of the tail; roentgenograms of the skeleton were obtained, and photographs were taken. A later series of animals were given injections either intravenously or intraperitoneally of 1 cc. of a 2

per cent aqueous solution of alizarin red, with the intention of later studying cross sections of the long bones to compare the rate of growth in different cats as registered by the concentric rings of dye deposited with subsequent injections. The kittens were then anesthetized with intravenous pentobarbital sodium (receiving approximately 0.44 grain [0.03 Gm.] per kilogram of body weight), and the head was shaved and cleansed with soap and water. With the use of a strict aseptic technic, the skin of the head was incised for 3 cm. at the vertex and a button of bone 1 cm. in diameter was removed by means of a trephine from the midline of the skull, thus exposing the dura and sagittal sinus. The button of bone was discarded. A Horsley-Clarke stereotaxic instrument was then accurately fixed to the head and the electrode carrier placed according to predetermined coordinates for the localization of the pineal gland. Without incising the dura, a monopolar electrode, 0.6 millimeter in diameter, insulated except at the tip, was passed through the sagittal sinus, along the falx and into the pineal gland, and adequate galvanic current and electrode manipulation were then used to coagulate and destroy completely this structure. The other electrode was placed on the tongue. Thus, no portion of the brain other than the pineal gland was damaged by the electrode, save the splenium of the corpus callosum, through which the electrode passed to reach the pineal gland. The skin was closed with metal clips, no other dressing being used. The animals were given physiologic solution of sodium chloride subcutaneously and were allowed to recover for twenty-four hours in an electrically heated warm box. At the end of that period they were usually ready to eat and drink.

Of a total of 71 cats, comprising nineteen litters, used so far in this investigation, 41 were males and 30 were females. None died from the effects of the operation, and there were no postoperative infections. An occasional animal had dilated pupils for a few days after operation. Six animals were found to have been incompletely pinealectomized, and others died of various causes before reaching maturity, when full use of their records could be made, so that their value has been vitiated so far as this report is concerned. Autopsy studies have been made on animals of all ages, up to twenty-two months after operation. Weekly weights and measurements were recorded; illnesses or feeding difficulties were noted, and behavior characteristics were observed frequently. The roentgenograms, photographs and injections of alizarin were repeated from time to time throughout the lives of the animals. Therefore at any time when autopsy was performed, there was available a complete case history of each animal. There are 14 cats now under observation in the laboratory, but this number, as well as other data contained in this report, will necessarily vary from time to time as the study of the problem continues.

During the early months after operation the female cats showed nothing unusual in their behavior, and, as shown by vaginal smears as well as observation of their sexual behavior, the pinealectomized and the control animals experienced the first estrus at approximately the same age, that is, at 13 months. At that time they were all successfully mated with a pinealectomized male. Several succeeding estral cycles

with pregnancy were observed, and autopsies on 3 cats, twenty-two months after operation, revealed 3 midterm fetuses in the uterus of each cat.

All kittens of both control and lesion mothers were sired by pinealectomized males. In no case did the litters contain more than 3 kittens, there being a total of 24 kittens of the second generation. At birth the kittens were small and weak and, in all but one or two instances, unable to nurse. Feeding whole cow's milk with a medicine dropper was uniformly unsuccessful, and all but 2 kittens died within forty-eight hours. One, a male kitten of a control mother, remained alive until the age of 8½ weeks. His mates died shortly after birth, while he grew steadily and remained healthy. However, he was found dead in the cage one morning, and autopsy did not reveal the cause of death. The other kitten, now 11 weeks old, is a female; its mates died the day after birth, and this cat, of pinealectomized parents, is thriving and healthy.

The control mother cats had an adequate milk supply, were attentive to their offspring and attempted to make them nurse, but the kittens seemed too weak to nurse though they were born at full term. The pinealectomized mothers were surprisingly different in their attitude toward their kittens. They were worried and restless after delivery, and paid but little attention to the litter, frequently covering them with straw and otherwise ignoring them. They exhibited little of the maternal instinct seen in most mother cats and made infrequent or feeble attempts to get the kittens to nurse. Indeed, their milk supply was deficient: in no case were the breasts as swollen and pink or the nipples as large and prominent in the pinealectomized mothers as in the controls. One lesion mother failed completely to show any changes in the breasts at parturition. Another pinealectomized female showed inadequate attention to her litter and lost 2 kittens thirty-six hours after delivery. In an attempt to save the remaining kitten she was given 10 units of prolactin for four successive days. Her milk supply became moderately increased; she remained with her one kitten for longer periods, and it thrived fairly well. She continued to be restless, as before the administration of prolactin.

Females 10 and 11 were given at one time 0.25, 0.5, 1 and 1 cc. of antuitrin-S (a preparation containing gonadotropic substance from the urine of pregnant women) on four successive days. Estrus resulted, with succeeding pregnancy, in female 11 (pinealectomized), but in female 10, the control, estrus was not produced. The 3 kittens born to female 11 in this instance were dropped in rapid succession and were probably three or four days short of full term. All the kittens died shortly after birth.

Until the age of 7 or 7½ months, the male cats all showed the same behavior characteristics. At that time, however, a change was noted in the pinealectomized animals. They became sullen, less playful and less like kittens and they preferred not to be petted. In handling them one felt they were not to be trusted, for they occasionally clawed or bit the attendants. This was not true of the controls; they were the usual pets until the age of 12 or 13 months, when they first showed

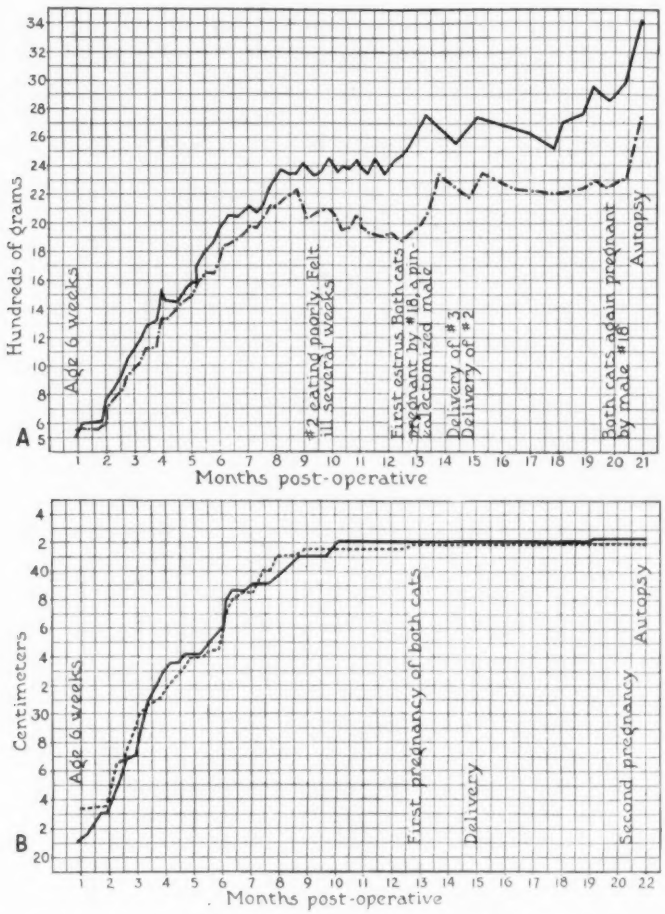

Fig. 1.—*A*, this chart shows a comparison of weights of 2 litter mate female cats, cat 3 being the control (solid line) and cat 2 the pinealectomized animal (line of dots and dashes). Note the equality of weights during the first ten months of life, when the rate of growth is most rapid.

B, this chart shows a comparison of the crown-rump lengths of the female cats the weights of which are charted in *A*. Cat 3, the control, is represented by the solid line; cat 2, the pinealectomized animal, by the broken line. Their skeletal growth progressed at equal rates throughout their lives.

signs of maturity. At 7 to 8 months not only were the pinealectomized males of larger bony frame, but their external genitalia were larger, erections were frequent, the tomcat mating call was first heard and they showed active interest in females. The hair about the head lengthened, giving their faces a broader appearance. These males were at all times sexually potent; 2 of them remained in a state of constant sexual excite-

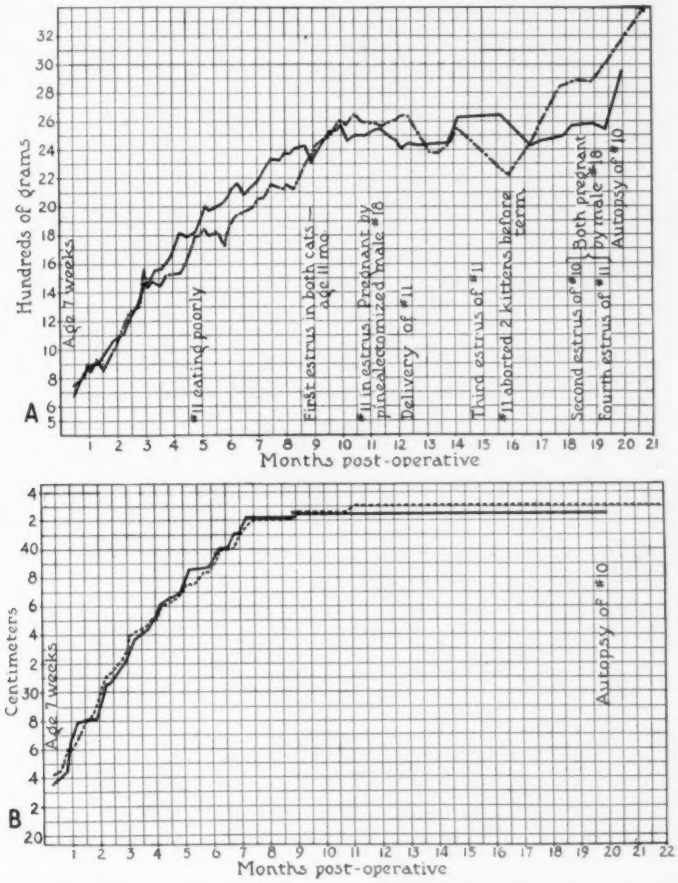

Fig. 2.—*A*, this chart shows a comparison of the weights of litter mate female cats 10 (the control, solid line) and 11 (the pinealectomized cat, line of dots and dashes). These animals were litter mates of male cats 15, 17 and 18. Note that the only practical differences in their weight growths occurred with the advent of pregnancy.

B, this chart shows a comparison of the skeletal growths of female cats 10 and 11, the weight chart of which is shown in *A*. The heavy line represents cat 10; the line of dashes cat 11.

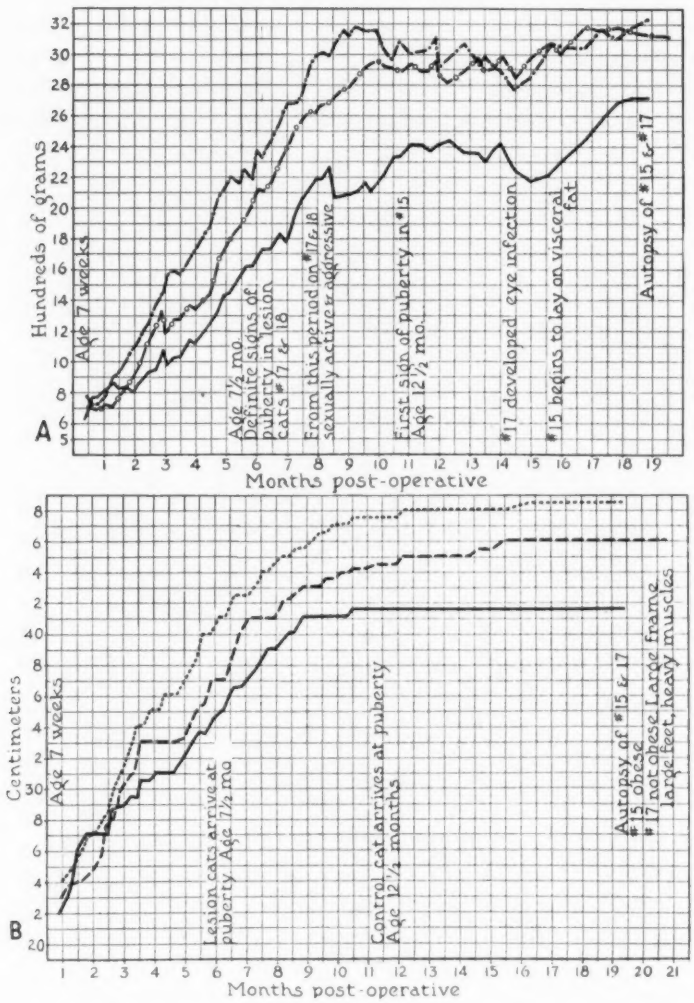

Fig. 3.—*A*, this chart shows a comparison of the weights of litter mate male cats 15 (the control, solid line); no. 17 (a pinealectomized cat, line of dashes and hollow circles) and no. 18 (a pinealectomized cat, line of dashes and solid circles). Note the greater weights of pinealectomized animals 17 and 18 at the time of puberty. Note also that cats 17 and 18 continued to grow heavier for three months after puberty.

B, this chart shows a comparison of the skeletal growths of control animal 15 (solid line) and pinealectomized animals 17 (line of dashes) and 18 (dotted line). Note that skeletal growth continued longer and was eventually greater in the pinealectomized animals.

ment and would attempt coitus with half-grown kittens of either sex or with adult females not in estrus. One pinealectomized male aged 5 months showed recognition of adult females, though he showed no signs of attempt at copulation.

Up to the time of puberty there was no difference in weight between the female control and the pinealectomized cats. With the advent of pregnancy the weights of the animals varied, but it was apparent that there was no significant difference in the actual body weight at any time. The lengths remained remarkably equal (figs. 1 and 2).

Since at least as early as 8 months of age the pinealectomized males showed definite signs of puberty, average lengths and weights have

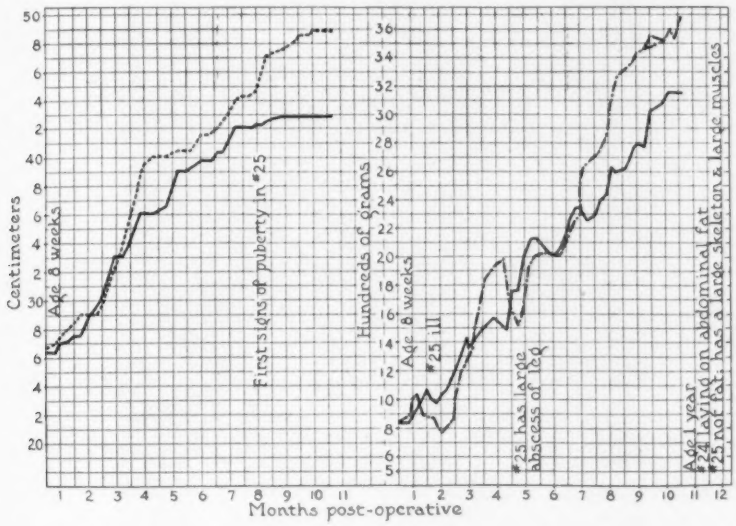

Fig. 4.—This chart indicates the growth in weight (at right) and length (at left) up to the age of 1 year of litter mate male cats 24 (control animal, solid line) and 25 (pinealectomized animal, dotted line). The skeletal growth persisted for a longer time in the pinealectomized male, and its weight at the age of 1 year was greater.

been computed for both control and lesion animals. The average length at 8 months for the control males was 39.7 cm.; that for the pinealectomized animals, 42.8 cm. The average weight of the control males was 2,040 Gm.; that of the lesion animals, 2,487 Gm. Until the time of maturity of the controls this disparity in size became more marked in most cases. After maturity the male animals of any one litter tended to show a leveling off in weight and length, though almost uniformly the lesion males remained the larger throughout the remainder of their lives. In 1 instance the control male, at the age of 16 months, weighed

more than his pinealectomized brother, though the latter had a larger skeleton. This control cat was extremely lazy, ate tremendous amounts of food; and the abdomen became bulging, sagging and full of great rolls of fat. Autopsy was never performed before 18 months of age, in order to make sure that the controls as well as the pinealectomized animals had reached a stable point of mature development (figs. 3 and 4).

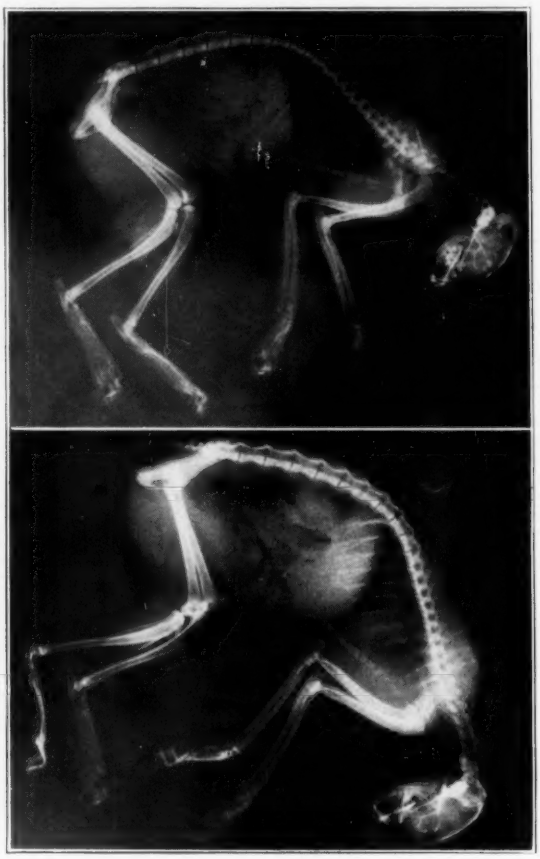

Fig. 5.—Roentgenograms of control male cat 15 (above) and pinealectomized male cat 17 (below). At the time these pictures were made these litter mate cats were 8½ months old, and both were growing. Pinealectomized cat 17 was already sexually mature, and it is obvious that he was the larger of the two cats. The epiphysial lines were still open.

Autopsies on entire litters were done on the same day. The weights and lengths of the animals were recorded, as well as the weights of some of the organs to be saved for histologic study. The females showed no gross significant differences. They were all healthy, well nourished

and free of vermin and parasites. The males were likewise in good condition. The pinealectomized males were heavier than their controls, though generally they had less intra-abdominal fat than their controls. One pinealectomized male had a massive skull, large feet, large leg bones and an over-all length 9.7 cm. greater than that of his control.

Alizarin was not administered to the first litters of cats studied, so that preparations of the bones or teeth have not been made from any mature animals examined at autopsy which were used in this report.

TABLE 2.—*Measurements on Four Male Cats* *

	Age, Mo.	Length of Head, Cm.	Length of Body to Fourth Lumbar Vertebra, Cm.	Length of Right Femur, Cm.
Control cat 15	9	8.4	1.6	10.4
Lesion cat 17	9	9.1	1.9	11.1
Control cat 24	11	9.5	1.9	10.1
Lesion cat 25	11	10.5	2.1	11.0

* In cats 15 and 17 the epiphysial lines were still open; in cats 24 and 25 they were closed, or nearly so, in all but a few locations.

Thin bone sections will be made from animals reaching maturity which have received injections of dye, and an attempt to reveal variations in growth will be made by a comparison of rings of dye deposited in the bone.

In none of the roentgenograms of cats were the epiphysial lines seen to be closed either earlier or later in the pinealectomized than they were in the control animals. The roentgenograms indicate plainly the large

TABLE 3.—*Average Weights in Grams of Fresh Organs of Cats on Which Autopsy Was Performed at 18 or More Months of Age*

	Female		Male	
	Control	Lesion	Control	Lesion
Brain	23.900	23.200	23.450	24.250
Thyroid	00.228	00.280	00.241	00.300
Adrenals (two)	00.413	00.380	00.470	00.515
Kidneys (two)	17.700	17.400	20.950	25.700
Ovaries (two)	00.295	00.265	.....	.....
Testes (two)	.....	.....	01.850	03.270
Heart	08.600	08.600	08.600	12.700

skeletal growth in the pinealectomized male animals (fig. 5), and table 2 summarizes three sets of measurements in 4 male cats.

Various organs were removed and fixed in solution of formaldehyde U. S. P. for microscopic study. These were: brain, pituitary gland, thyroid, adrenals, kidneys, gonads, pancreas, liver, heart, spleen, thymus, abdominal aorta, midthoracic portion of the spinal cord, right humerus and a tooth. Table 3 indicates the differences in weights of these organs in the control and lesion cats of the two sexes.

Histologic observations have been made to determine what, if any, are the morphologic differences in the special organs removed. In the brains of the pinealectomized cats, stained by the Weil technic, no degeneration anterior to the habenular nuclei could be traced. In 2 or 3 instances there was slight heat destruction of the corpus callosum and the underlying anterior quadrigeminal plate. The anterior lobe of the pituitary glands of all the male animals showed a preponderance of acidophilic cells, and the cells contained less cytoplasm than those of the anterior lobe of the female cats. There was, then, a difference in

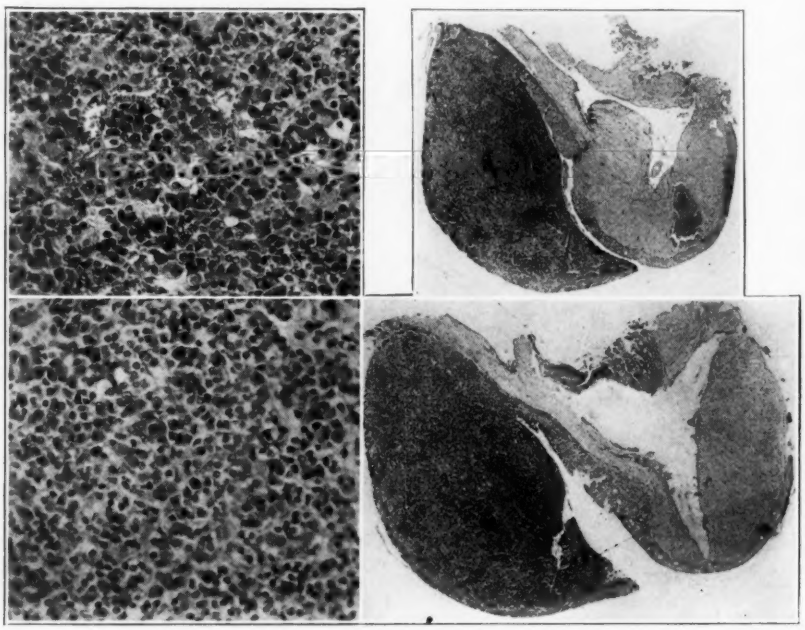

Fig. 6.—Photomicrographs of the hypophyses of litter mate male cats 15 (control, above) and 17 (pinealectomized, below). Cross sections, × 10. The histologic appearance of both is normal, although the cells in the hypophysis of control animal 15 stained darker; × 430.

the histologic appearance of the pituitary glands of the male and the female cats, but no difference between those of the pinealectomized and of the control animals of either sex. The female cats on which these observations were made were pregnant at the time of the autopsy. The pituitary gland of male control cat 15 was smaller than that of cat 17, his pinealectomized brother, and the posterior lobe of cat 17 was somewhat less cellular (fig. 6). No essential differences in the anterior lobe, pars tuberalis or pars intermedia existed between the pinealectomized and the control males. The thyroid glands showed no variation

from the normal in any animal; possibly there was evidence of more activity in the glands of the females, as shown by the generally higher follicular cells. In the cortex of the adrenal glands of the pinealectomized male cats there was an outer layer of large, clear, "frothy" cells, forming wide, short, open cords, which extended eight to ten

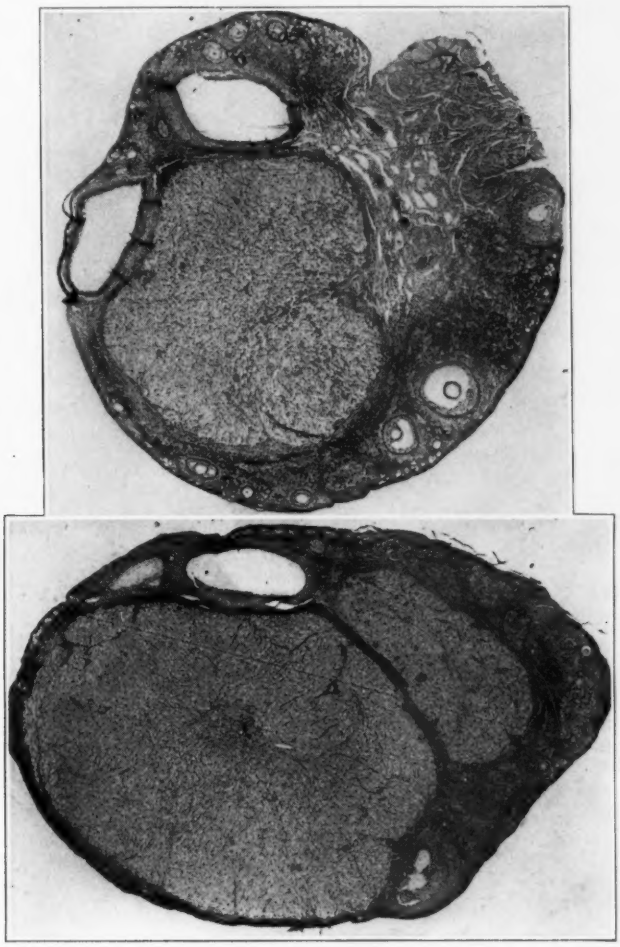

Fig. 7.—Cross section of the whole ovary of litter mate female cats 2 (pinealectomized, above) and 3 (control, below). There is no essential difference between them. Both ovaries show ripened follicles, ruptured follicles and old atretic areas. Magnification, × 25.5.

cells deep into the cortex. This was probably the zona fasciculata, though no well defined zona glomerulosa external to it could be seen. The palisade arrangement of the cortex was more marked in the males

than in the females. The medulla exhibited no variations in any of the cats. The kidneys, pancreas, liver, spleen, aorta and heart showed no changes from the normal in either sex. The thymus in all the females was in approximately the same state of degeneration; many lobules of

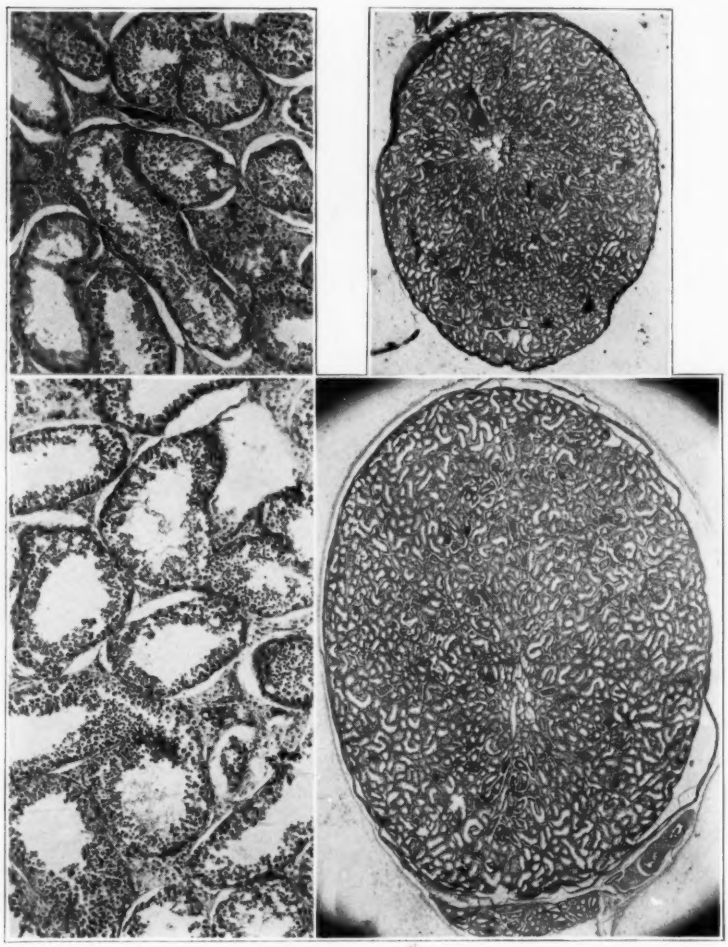

Fig. 8.—Above, a cross section of a testis of control male cat 15, at a magnification of × 10, with a high power section of the same testis at a magnification of × 105. Below, a testis of pinealectomized male cat 17, prepared at the same magnifications. In the lesion cat the tubules appear larger, with active spermatogenesis. The gross difference in the size of the testes, both cut through the greatest transverse diameter, is easily recognized.

well differentiated thymic tissue remained, however. The thymus of cat 17, a pinealectomized male, contained a larger proportion of connective tissue and fat, with small but well defined lobules of glandular

tissue. The ovaries showed little, if any, difference, a fact to be expected from the appearance of puberty at a uniform age, whether the cat was pinealectomized or not (fig. 7). In the females dying before puberty no differences could be demonstrated in the ovaries. In the case of 2 male cats dying at 5½ months of age, there was no difference between the histologic picture of the testes of the pinealectomized animal and that of his control. The tubules contained little or no lumen, and the cell layers were only two or three cells high. Since no animals have been killed at the stage when the pinealectomized males begin to show signs of puberty, all specimens available were those of adult cats in which the testes of both control and lesion animals showed active spermatogenesis. In the lesion cats, however, the tubules were larger and more contorted and had thicker walls. There was rather sparse interstitial tissue in lesion cat 17; spermatogenesis was everywhere in evi-

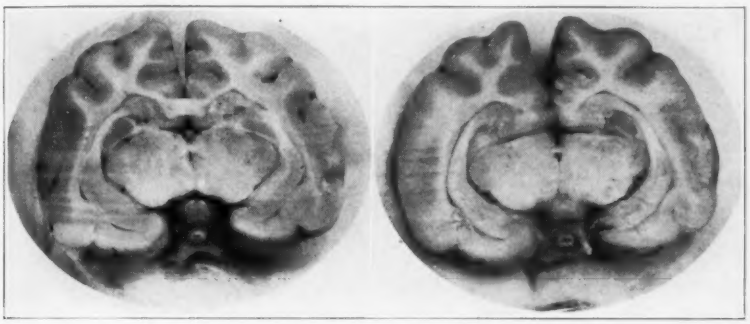

Fig. 9.—Cross sections through the fixed brains of male cats 15, left, and 17, right, to show the presence of the pineal gland in cat 15, the normal control, and the absence of the gland in cat 17, the pinealectomized animal.

dence, and the germinal epithelium, showing many mitotic figures, was five or more cell layers thick. In cat 15, his control, the tubules were smaller, and there was less active spermatogenesis, although this cat, too, had long since reached maturity (fig. 8).

In a series of 18 animals studied in 1936, 5 of 15 operated on were found at autopsy to have been incompletely pinealectomized. Since that time 1 female kitten, which died a few weeks after operation, was observed at autopsy to have an intact pineal gland. All of the animals on which this report is based were proved to be pinealectomized completely by gross and microscopic examination (fig. 9). Serial sections of the brain from the region of the pineal gland forward through the stalk of the hypophysis were made and stained by the Weil method. Examination failed to show any degeneration of fibers leading to the pituitary gland or other portions of the diencephalon. In 2 pinealec-

tomized cats there was evidence of slight heat destruction of the splenium of the corpus callosum and anterior portion of the quadrigeminal plate (fig. 10).

The midterm fetuses, the term fetuses and the older kittens making up the second generation have been prepared as an embryologic series. Through the newborn stage the fetuses showed no changes; all the organs, including the brain and the pineal gland, were normally immature. The organs of an 8½ week male kitten, born of a normal mother and a pinealectomized father, showed no abnormalities of the parenchymatous organs, brain or pineal gland, and the testes, with germinal epithelium only two or three cell layers thick, compared favorably with those of any cat of that age.

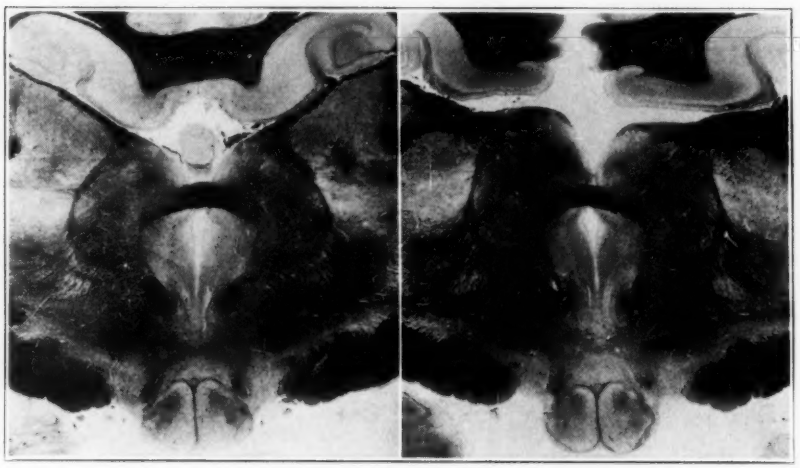

Fig. 10.—Left, a section through the region of the pineal gland in a normal cat, control male 15. Right, a section through the region of the pineal gland in pinealectomized female cat 2. This section was chosen since it shows, in addition to the absence of the pineal gland, a feature sometimes seen, local destruction of the corpus callosum where the electrode passed through it. Lateral to the pineal area there remains, on either side, a plexus of fine veins. Weil technic; magnification, × 10.

DOGS

Thus far, two litters of dogs have been used in this investigation. Three male dogs in one litter (father, thoroughbred wire hair terrier; mother, thoroughbred cocker spaniel) and 3 females of another litter, obviously of ordinary mongrel variety, have been prepared for observation. In each instance the dogs were well matched as to size and were able to live away from the mothers, though they were not yet weaned when they were operated on.

At the age of 4½ weeks the dogs were tagged for identification, weighed, measured from the external occipital protuberance to the base of the tail, photographed and given injections of 2 cc. of a 2 per cent aqueous solution of alizarin red.

One animal in each litter was chosen as the normal control. The other two were anesthetized by intravenous injection of pentobarbital sodium (0.44 grain per kilogram of body weight) and their heads shaved and cleansed with soap and water. With use of a careful aseptic technic, the skin of the vertex was incised; the muscles were retracted, and a circular area of bone, approximately 3 cm. in diameter, was removed. With careful retraction the occipital lobes were separated; the falx was cut deep to the sagittal sinus, and the splenium of the corpus callosum was divided. Up to this point the operation was essentially bloodless. However, on removing the pineal gland with fine forceps there was

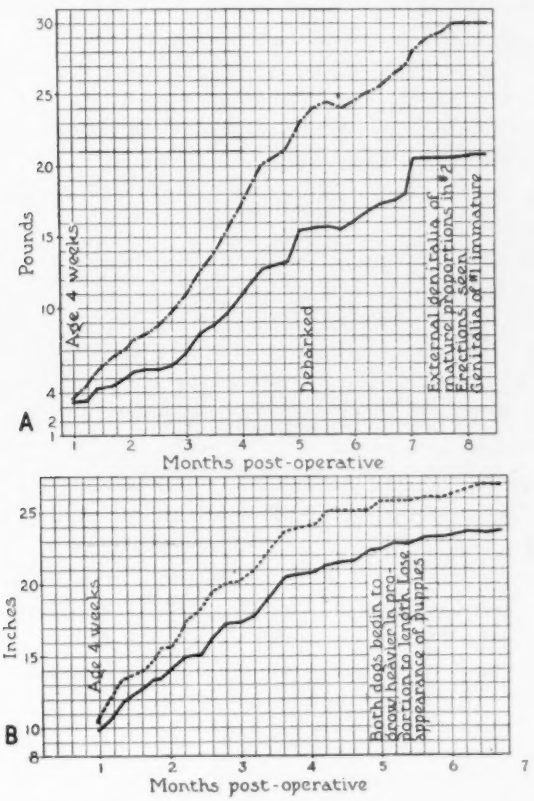

Fig. 11.—*A*, this chart indicates the comparative weights of 2 litter mate male dogs up to the age of approximately 9 months. There was an obvious increase in the weight of the pinealectomized animal, dog 2 (line of dots and dashes) over the control animal, dog 1 (solid line).

B, this chart indicates the skeletal growth of litter mate male dogs 1 and 2. Note the early and sustained gain in the pinealectomized animal (dog 2, dotted line).

usually enough avulsion of the attached veins to produce sharp hemorrhage. This was controlled by moist cotton sponges and irrigations of warm physiologic solution of sodium chloride. The subcutaneous tissues were closed with silk, and the edges of the skin were approximated with metal clips. Physiologic

solution of sodium chloride was given subcutaneously, and after a few hours in a warm box the animals were sufficiently recovered to drink milk.

There were no instances of postoperative death or infection. One male pup had severe epileptiform seizures three months after operation and was therefore chloroformed. The pineal gland was found to have been completely removed, but there was a dense scar formation between the falx and dura and the adjacent cortex. One female dog was blind after the operation, and it was necessary likewise to chloroform the animal. A large hemorrhage was observed in the third ventricle and over the corpora quadrigemina. There are remaining, then, 4 dogs: 2 males and 2 females, 1 of each sex acting as a control and the other being pinealectomized. Weekly weights and measurements have been made; photographs and injections of alizarin have been repeated from time to time, and the behavior of the animals has been recorded, so that with the dogs, as with the cats, a chronologic case history has been maintained for each animal.

At present all the dogs used in this investigation are still living. At 10 months the control male was 24.5 inches (62 cm.) long and weighed 21 pounds (9.5 Kg.); the pinealectomized male was 27.5 inches (69.8 cm.) long and weighed 33 pounds (17.2 Kg.). At the age of 7½ months the lesion animal began to appear mature; the scrotum became pigmented and pendulous, the testes were large and freely movable and frequent complete erections were noted. At 10 months he had the appearance of a mature dog, but showed no signs of active sexual interest (fig. 11). The control dog, at 10 months of age, had genitalia approaching mature proportions, but smaller than those of his lesion brother. At 5 months of age the control female was 20.25 inches (51.5 cm.) long and weighed 12½ pounds (6.1 Kg.). The lesion female was 20.5 inches (52 cm.) long and weighed 15 pounds (6.8 Kg.); both were obviously still prepubertal. More complete studies of these animals will be reported at a future date.

SUMMARY

The pineal gland has been extirpated in young rats, cats and dogs, and adequate litter mate controls of each sex have been used for comparison of their development. As nearly uniform laboratory conditions as possible have been maintained during the growth period of these animals.

No behavior changes were noted in the pinealectomized rats. Sexual maturity was attained at the same age in both control and lesion animals. There was some indication of increased somatic development in the males at puberty.

There were no differences in somatic or sexual maturation in the female control and the lesion cats. Both experienced normal estrus, and

both had normal pregnancies; but their offspring, sired by pinealectomized males, were weak, and of 24 kittens only 2 lived more than forty-eight hours. The pinealectomized mothers showed a lack of maternal instinct and lactated inadequately. The pinealectomized males matured sexually four to five months earlier than their controls and showed a precocious somatic development, still being larger than their controls at the time of full maturity of the normal cats. The lesion males were less playful, more aggressive and more belligerent than their controls.

Second generation cats, either as midterm or term fetuses or as cats several weeks of age, did not show any gross variations from the normal animal of the same age.

Serial sections of the cat brains did not show degeneration anterior to the habenular nuclei. No significant difference was noted between the mature control and the lesion animals in the histologic picture of the thyroid, adrenals and ovaries. The testes and hypophyses of the pinealectomized males were larger than those of the control males, and the histologic appearance of these organs reflected the gross state.

One pinealectomized male dog outstripped his control both as to sexual development and body size before 10 months of age.

This report sets forth the results of extirpation of the pineal gland in young mammals, the animals being allowed to reach maturity with continuous observation of their somatic and sexual growth, as well as of their behavioristic and reproductive characteristics. This investigation is still in progress, and the data must necessarily change therefore from time to time. No arbitrary interpretation of our present results can be stated; no statements of definite proof of any special function of the pineal gland can be made. It may be postulated, on the basis of the results here presented, that the pineal gland has a glandular function, probably endocrinal early in life in mammals, and that its function exerts through a yet undescribed process an influence on the sexual and somatic development of the immature animal.

MODIFICATION OF GUDDEN METHOD FOR STUDY OF CEREBRAL LOCALIZATION

ALF BRODAL, M.D.
OSLO, NORWAY

In recent anatomic studies of the central nervous system experimental methods for investigation of localization and interconnections of different regions have been extensively employed. Such problems may in some instances be solved by application of the Marchi technic. Usually, however, the retrograde cell changes must be studied, either early chromatolysis or the late changes, consisting of atrophy and loss of cells. In studying the problem of localization within the olivocerebellar connections, I found that none of these methods proved satisfactory. In order to find, if possible, a more suitable method, I therefore undertook a systematic investigation of the retrograde changes in the cells of the inferior olive following lesions of the cerebellum. A modification of Gudden's method was chosen which gives more definite and exact results than those previously mentioned, and, at the same time, avoids for the most part the drawbacks of the original method. A report on the procedure and the results which can be achieved with it were thought worth publication, since the method seems to be generally applicable. As far as can be seen, this problem has hitherto not received attention.

In the following pages the cell changes in the inferior olive will be briefly mentioned, and the results of the various methods in question discussed. On the basis of the results in the olive, the general applicability of the method will be discussed and demonstrated in part.

The cell changes in the inferior olive of mice and rabbits of different ages and at varying intervals after the operation were described in detail in a previous paper,[1] in which some of the literature on this problem was discussed. In the present article these changes will be considered only as far as is necessary for discussion of the present problem.

In adult mice and rabbits the earliest changes in the cells of the inferior olive are seen approximately on the fourth day after a lesion

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From the Anatomical Institute, University of Oslo.

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Dr. Jan Jansen gave valuable advice in this study.

1. Brodal, A.: Experimentelle Untersuchungen über retrograde Zellveränderungen in der unteren Olive nach Läsionen des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:646, 1939.

of the cerebellum. At this time nearly all the cells in a circumscribed part of the contralateral olive show moderate, atypical tigrolysis, which seems to begin in the central part of the cytoplasm. During the following days the tigrolysis increases; at the same time the nucleus and the cell gradually decrease. The nucleus is not displaced toward the periphery of the cell. This picture is seen in nearly all cells in the affected part of the olive about eight days after a sufficiently large lesion, and represents the maximum retrograde reaction in these cells. Already at this time cells may appear as "cell shadows" or as very pale, shrunken nuclei, surrounded by a scanty mass of pale cystoplasm. Such cells, obviously disintegrating, are seen in increasing numbers during the following days. At the same time the total number of cells is gradually reduced. About sixteen days after the operation from one third to one half of the cells have disappeared, and disintegrating cells are relatively seldom seen. At later stages approximately the same degree of cell loss is noted, indicating that most of the cells which disintegrate acutely do so within sixteen days after the lesion.

The cells which do not disappear undergo a change, but in another way: They grow steadily smaller; some recover some of their Nissl bodies; others remain pale. These cells thus become atrophied, and after some time are extremely reduced in size. In the later stages there is a slight increase of the glia cells in places where some of the nerve cells have disappeared. The ratio of disintegrating cells depends to a certain degree on the depth and extension of the cerebellar lesion. When the cortex of a part of the cerebellum has been ablated but the central white matter is left intact, about one third to one half of the cells in the corresponding region of the olive will perish. After lesions which do not destroy all the cortex of a great part of the cerebellum, single normal cells will always be seen among those which are pathologically changed.

From the point of view of the application of these changes in the olive to studies of the olivocerebellar connections, the following must be said: The early changes, the retrograde reaction (corresponding to *primäre Reizung* in peripheral neurons), as seen about eight days after the lesion, have little resemblance to the typical *primäre Reizung* which Nissl[2] described.[3] The tigrolysis is the only common feature, but the cytoplasm has not that diffuse, nearly homogeneous appearance seen in the retrograde reaction, for example, of the cells of the facial nucleus. There is no deviation of the nucleus, and the cell shrinks rather than swells. The cells of the olive being relatively small, most of the Nissl bodies

2. Nissl, F.: Ueber die Veränderungen am Facialiskern des Kaninchens nach Ausreissung der Nerven, Allg. Ztschr. f. Psychiat. **48**:197, 1892.

3. The term *primäre Reizung* is used here only for cells presenting all the typical signs of this change.

often being normally aggregated at the periphery, and showing considerable variation in size and tigroid content, it is obviously difficult to distinguish normal from definitely pathologic cells. This is relatively easy only when large parts of the olive are affected, i. e., when the cerebellar lesion is deep and extensive. Even then, determination of the limits of the areas of change is uncertain, and small areas of alteration cannot be made out at all. In addition to these difficulties, artificially light cells are often seen. Some of these probably are cells cut tangentially. In some cases (especially in cats) all the cells of the deepest portions of the olive appear very pale, the Nissl bodies being almost lacking and the limits of nucleus and cytoplasm being indefinite. Probably this is due to slow penetration of the fixative (96 per cent alcohol).

As far as the inferior olive is concerned, there can thus be no doubt that study of the early retrograde changes in adult animals is not a method that yields satisfactory results.

Better results can be obtained by allowing the animals to live two or three months longer. The late cell changes which appear in the olive after that time, characterized by loss of cells and atrophy of the remaining cells, may seem easy to ascertain; yet the results often prove doubtful. In the first place, the estimation of a loss of one third to one half the normal number of cells is difficult, as the cells normally show great variations in density and lie relatively far apart. Moderate loss of cells following smaller lesions cannot be detected for this reason. However, the cell atrophy may in some cases be so prominent that there is no difficulty. Unfortunately, the value of this feature is often reduced or completely abolished, owing partly to the fact that the cells normally show considerable variations in size but still more to the frequent appearance of artificially shrunken cells (*chromophiler Zustand* of Nissl). Such cell specimens often cannot be distinguished from atrophied cells. According to Droogleever-Fortuyn,[4] Scharrer [5] and others, these artefacts are due to mechanical effects on the cells of handling the brain post mortem. Fixation by injection is said to prevent their appearance, but this is not always practical. In the olive these shrunken cells are especially frequent in the most superficial parts and are apt to vitiate the interpretation of a series.

An example of the results achieved in the olive by this method is shown in figure 1 *A*.

Between the arrows is an area which, as compared with that on the normal side, shows loss of cells; approximately one half have disappeared. Nearly all the remaining cells are considerably diminished and atrophied.

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4. Droogleever-Fortuyn, A. B. D.: Histological Experiments with the Brain of Some Rodents, J. Comp. Neurol. **42**:349, 1927.

5. Scharrer, E.: On Dark and Light Cells in the Brain and the Liver, Anat. Rec. **72**:53, 1938.

The normal variations in the density of the cells are also clearly visible. This section is one of a series from a rabbit in which the paraflocculus had been removed on one side. The animal was killed three months after the operation.

As this procedure also proved unsatisfactory, although the results were better than with the method first discussed, it seemed advisable to try to find a more practical method. A modification of Gudden's method proved to be the best, as has already been mentioned.

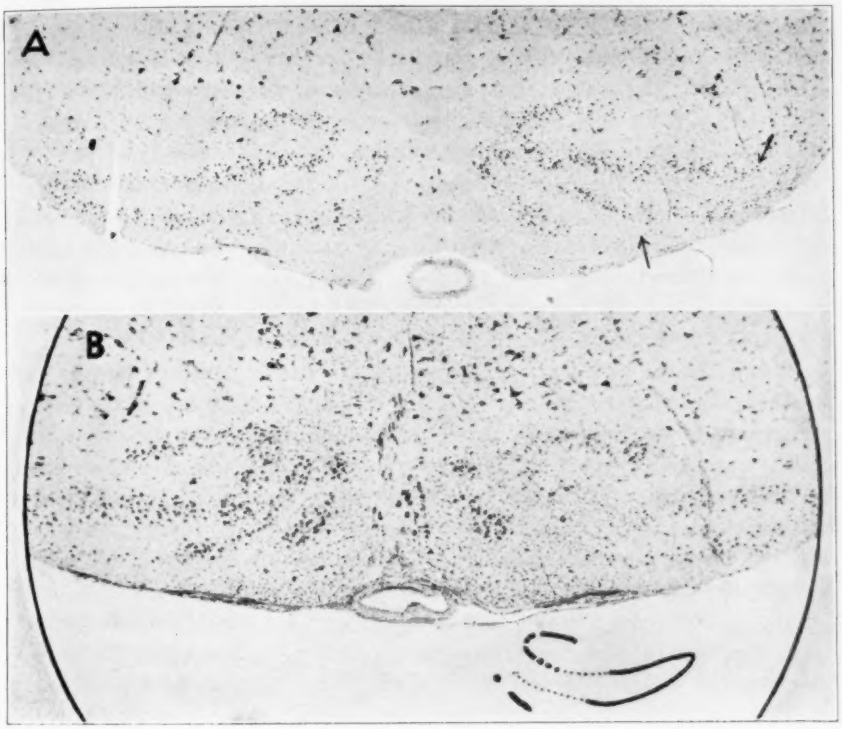

Fig. 1.—*A* (× 20) section through the inferior olive of an adult rabbit, killed three months after extirpation of the paraflocculus on one side. In the contralateral olive, between the arrows, there are loss of cells and atrophy of the remaining cells. *B* (× 32) section through the inferior olive of a rabbit, 11 days old at the time of operation and killed eight days later. At the operation part of the lobulus ansoparamedianus was removed on one side. In a considerable portion of the contralateral olive practically all the cells have disappeared. See the diagram below. Thionine stain.

Gudden [6] and his pupils operated on the animals from one to two days after birth, and kept them alive for many weeks, or even months.

6. Gudden, B.: Experimentaluntersuchungen über das peripherische und centrale Nervensystem, Arch. f. Psychiat. **2**:693, 1870.

After this time, all cells the axons of which have been damaged have disappeared, as have also the central and peripheral portions of the axons sectioned. (Gudden originally did not realize that these changes were retrograde. To von Monakow [7] is due the credit of having shown this to be true.) This complete disappearance of cells, which does not take place after corresponding lesions in adult animals, constitutes the great advantage of Gudden's method, which has been extensively employed in experimental research on the brain. When the animals are kept alive as long as was Gudden's practice, however, the intact parts as a rule are considerably displaced in relation to each other, and there is apt to be shrinkage, especially when larger regions are affected. These displacements may cause great trouble in judging which parts are altered. Together with the slight resistance offered by newborn animals, they constitute the chief drawback to the method of Gudden.

It is probable that these unfortunate displacements may be avoided by using newborn animals which are killed earlier than was the practice of Gudden; the shorter the period the animals are kept alive after the operation the better the results. These displacements are caused by the continued growth and myelination of the intact fibers, while the damaged fibers disappear completely. The accompanying glial proliferation may eventually cause shrinkage of the tissue. It would be advantageous to kill the animals immediately after the cells have disappeared. The literature shows that Gudden and his pupils were aware of the rapid cell disintegration which takes place in newborn animals. However, the technic of that period did not permit finer structural analysis. After the Nissl technic had become generally employed and after Nissl's [8] demonstration of the *primäre Reizung* and its application to studies of localization, the Gudden method apparently was little used, and authors who have used newborn animals have continued to let them live for a long time. Systematic observations on the earliest period at which the cells disappear in newborn animals, have, as far as I know, been published only by Spatz [9] for the anterior horn cells in rabbits. Although Gudden and his pupils, as well as Nissl and other authors, have drawn attention to the striking difference in reaction of the nervous systems of the

7. von Monakow, C.: Ueber einige durch Exstirpation circumscripter Hirnrindenregionen bedingte Entwickelungshemmungen des Kaninchengehirns, Arch. f. Psychiat. **12**:141, 1882.

8. Nissl, F.: Ueber eine neue Untersuchungsmethode des Centralorgans speciell zur Feststellung der Localisation der Nervenzellen, Centralbl. f. Nervenh. u. Psychiat. **17**:337, 1894; footnote 2.

9. Spatz, H.: Ueber die Vorgänge nach experimenteller Rückenmarksdurchtrennung mit besonderer Berücksichtigung der Unterschiede der Reaktionsweise des reifen und des unreifen Gewebes, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1921, supp., pp. 49-354.

newborn and of the adult, and the cause of this difference has been frequently discussed (e. g., by Gudden,[6] Mayser [10] and Forel [11]), the problem of how long after birth the type of reaction seen in the newborn prevails seems not to have been investigated. If this type of reaction should last for some time after birth it would be of great advantage in experimental investigations. In order to settle this question with regard to the olive and to determine the time at which the cells disappear experiments with young animals were undertaken.[1]

The results obtained may be summarized as follows: The retrograde cell changes in the olive of newborn animals differ considerably from the changes seen in adults. In mice and rabbits from eight to eleven days old at the time of operation, the retrograde reaction consists of tigrolysis and diminution in cell volume, as seen in adult animals. The cytoplasm, however, acquires a diffuse, nearly homogeneous appearance; the Nissl bodies appear "dusty," reminding one more of the changes in the peripheral motor cells than is the case in adults. Furthermore, the nucleus is displaced to the periphery of the cell and appears pale, flat and reduced. (Normally the nucleus has a peripheral position in the cells of newborn animals, but far less so than in the retrograde reaction.)

After a lesion which approximately reaches the central white matter of the cerebellum, nearly all cells in a corresponding part of the contralateral olive pass this stage in the course of three to four days. Later, they disintegrate rapidly. After six days about half the cells have disappeared; after eight days only a few show diminution, and tigrolytic cells can be seen, as well as a few normal cells. This loss is accompanied by an intense increase of the glial elements. In newborn animals, therefore, practically all cells disintegrate; only a few become atrophied. Figure 1 *B* demonstrates these changes. The photograph was taken from the olive of a rabbit, operated on when 11 days old and kept alive for eight days after the operation. An extensive portion of the right lobulus ansoparamedianus was removed. In a part of the contralateral olive (right side of the figure) a practically total loss of nerve cells is noted, whereas the glia is heavily increased.

Important is the fact that there is a gradual transition from this type of reaction to that found in adult animals. In rabbits 3 weeks old at the time of operation, there is still loss of cells nearly as complete as in animals 11 days old, with a slightly greater number of atrophied cells. The glial reaction is still abundant. As the changes progress a little less rapidly, the animals are best kept alive for eleven to twelve days in order to achieve complete disappearance of the cells.

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10. Mayser, P.: Experimenteller Beitrag zur Kenntnis des Baues des Kaninchen-Rückenmarks, Arch. f. Psychiat. **7**:539, 1877.

11. Forel, A.: Einige hirnanatomische Betrachtungen und Ergebnisse, Arch. f. Psychiat. **18**:162, 1887.

The aforementioned conditions make it possible to use animals 10 to 12 days old and to kill them eight to twelve days after the operation. This method has proved satisfactory.

As compared with the methods discussed earlier, it has the following advantages: 1. Obviously, the total loss of cells achieved by this procedure is easier to observe and determine than the atypical picture of retrograde reaction in adult animals or the partial loss of cells with atrophy of the remainder, observed after a greater lapse of time. This is especially striking when the changes are limited to a smaller region of the olive. In this way the method permits identification of the projection areas of smaller cerebellar regions than do the others.

2. As myelination is not yet complete, the cells are denser. Loss of cells, particularly incomplete loss following a small lesion, is therefore also better observed.

3. In the peripheral parts of the altered regions of the olive, some slightly changed cells showing retrograde reaction will usually be seen. This, too, facilitates determination of the limits of the affected areas, as these cells differ from the normal cell type far more than do the cells showing retrograde reaction in adult animals. This, however, will be the case only when the animal is killed a very short time after the majority of cells have disappeared. As there is individual variation in regard to the rate of the changes, these cells cannot always be seen.

4. The intense glial reaction clearly marks the places where the nerve cells of the olive band have disappeared (figure 1 *B*).

5. Artificially shrunken cells are less often encountered, and are also less disturbing, than when the other methods are employed.

6. The preparations are smaller, and are therefore more rapidly and cheaply prepared. The results of the experiment are secured sooner than when the method of atrophy is used.

In spite of the decided advantages of this method, it has some drawbacks. These are the same as in the original method of Gudden,[6] but the modifications proposed here will, to a great degree, do away with the disadvantages.

The secondary displacements, the chief objection to Gudden's method, are almost completely avoided. As the animals live only a few days, the progress in myelination during this time is moderate. Neither is there any shrinking, as the disintegrated cells and fibers are not yet fully resorbed. Reduction of the volume of the olive can be observed only when the changes are extensive.

The other chief disadvantage of Gudden's method is the low resistance of newborn animals. These are wholly dependent on the mother, who often neglects them or kills them by biting or treading on them.

The older the young animals are at the time of the operation, the more favorable the conditions will be in this respect. Animals from 10 to 20 days old can stand rather extensive operations, provided there is no severe hemorrhage. They are highly susceptible to bleeding. Also, animals of this age are not as easily bitten or mishandled by the mother. Of importance in this connection, of course, is the condition of the animals after the operation; if not too much weakened they will usually survive. It has proved advantageous not to operate on all the animals in one litter at the same time, so that the mother always has some normal young. Although loss of some newborn animals can scarcely be avoided, this loss will, on the grounds mentioned, be considerably less than when with Gudden's method. Gudden [6] claimed as advantages of this method that the newborn are hairless, that anesthesia is not necessary and that the blood coagulates rapidly. The last-mentioned condition applies also to animals 10 to 12 days old; with regard to the other points, however, differences exist. Anesthesia must be used with the older animals. It should be pointed out that young animals are highly susceptible to an overdose of ether. Cessation of respiration on this account is often fatal, whereas in adult animals asphyxia can generally be overcome by artificial respiration. The hair of the animals, of course, causes trouble.

On the other hand, the brain is larger and can be more easily handled during the operation. Identification of the parts is therefore facilitated, and the lesion is easier to place as intended, although this is more difficult than in adult animals. A condition which contributes to make the exact delimitation of the lesion uncertain is the softness of the brain tissue. This will often cause the zones adjacent to the extirpated parts to be displaced or drawn out when the lesion is made.

A peculiar characteristic of the reaction to damage of the central nervous system of the newborn animal is its great power of healing without leaving a scar, a feature of which Gudden was aware and which has been verified by various authors. Spatz [9] has shown that this is due to a difference in the process of resorption of the destroyed parts in newborn and in adult specimens. The glia cells are more dense in newborn animals, and they alone bring about repair, as there is little myelin present. In adults, on the other hand, in which the glia cells lie far apart and there are abundant masses of myelin, mesodermal elements also take part in the resorption and repair of the tissue. In this case, therefore, the result is a scar of connective tissue, whereas in newborn animals only a fine glial membrane indicates the place where the continuity of tissue was once broken. From an experimental point of view, this is a disadvantage, making difficult identification of lesions, especially small ones. In this respect animals from 10 to 20 days old are more suitable than newborn animals. As a rule, at this age some connective

tissue takes part in the repair and will thus mark the limits of the lesion. The aforementioned difficulties are especially apt to arise when extirpations are performed with sharp instruments. With use of thermocautery the destroyed parts will remain *in loco* and thus facilitate the determination, as the more abundant disintegrated masses are not yet absorbed after from eight to twelve days. Thermocauterization, on the other hand, has disadvantages, which, however, will not be discussed here.

In connection with the type of reaction at the site of the lesion in the nervous system of the newborn, another feature should be mentioned, which may sometimes cause confusion. Small cavities, the *Nebenpori* of Spatz, may sometimes be seen far from the lesion. They are limited by a fine glial membrane (membrana glia limitans accessoria, Spatz) and are, according to this author, due to softenings of vascular origin. When these cavities are located in the systems under investigation they may spoil a series. However, they are not frequently encountered.

As will be seen, the method here proposed also has its drawbacks. As far as I can see, these are more than compensated for by the great advantage of the method: the distinct cell changes in the olive. The main requirement in studies of localization is to obtain as clearcut and definite changes as possible in the system under investigation.

A problem of considerable interest is whether the method here proposed will prove to be superior to other methods in the study of localization in other parts of the nervous system. This question will be discussed briefly. The conclusion will depend on whether the retrograde cell changes in newborn and adult animals in the systems in question show conformity with those in the olive.

The literature shows that the retrograde cell changes in different neuronic systems show in part considerable variations in regard to the morphologic character of the cell changes, the rapidity of the reaction and the ultimate result, as well as the type of animal employed and the intensity of the lesion. (These matters are more fully discussed in the paper previously mentioned.) In the peripheral motor and sensory neurons a more or less typical picture of *primäre Reizung* is usually seen in the early stages. In these cases the original Nissl method [8] will be most suitable.

In the central neuronic systems, however, conditions are different. Sometimes the typical *primäre Reizung* may be encountered, but more often there appears only more or less atypical tigrolysis in the cytoplasm several days after damage to the axon. According to meager data available from the literature concerning this point, the later course of the cell reaction is analogous to that observed in cells of the olive: Some of the cells disappear completely; others do not recover, but atrophy rapidly.

It seems probable, therefore, that the problems arising in investigations on localization in other central neuronic systems will be the same as those met in studying the olive.

Kohnstamm [12] and other authors have utilized early retrograde changes in studying the fiber connections of the brain stem. However, this procedure (*die tigrolytische Methode*) has not been extensively employed, which indicates that the method is not satisfactory. Allen's [13] results are significant in this connection. This author expressed the opinion that he saw "chromolysis" in the cells of the nucleus tractus solitarii after section of the spinal cord. However, control experiments showed that such cells are normally present in about the same number. Therefore, no conclusions could be drawn from these observations. The tigrolytic cells were interpreted by Allen as fatigued specimens. Allen, like several authors before him, found evidence that fatigued cells are poorer in Nissl bodies and paler and larger than resting cells. As probably all gray masses always contain some fatigued cells, great caution is required in drawing conclusions concerning retrograde reaction in gray masses the cells of which do not show retrograde reaction with the typical picture of *primäre Reizung*. (As is well known, the appearance of this characteristic change is not sufficient to prove that the axon of the cell has been damaged.)

As is true in the olive, study of the late retrograde changes—cell loss and atrophy—seems to give better results than the "tigrolytic method" in other central neuronic systems. Le Gros Clark,[14] Walker [15] and others have obtained satisfactory results with this method for the thalamus, as have Bodian [16] and Poljak [17] for the external geniculate body. However, there is reason to believe that in still other cases the "atrophy method" will not yield satisfactory results and that the method here proposed will be preferable. This will be true only in the geniculate body. However, there is reason to believe that in still other cases the "atrophy method" will not yield satisfactory results and that the method here proposed will be preferable. This will be true only in systems in which the same characteristic differences exist between the

12. Kohnstamm, O.: Studien zur physiologischen Anatomie des Hirnstammes: III. Die tigrolytische Methode nebst Beispielen für ihre Anwendung, J. f. Psychol. u. Neurol. **17**:33, 1910.

13. Allen, W. F.: Experimental-Anatomical Studies on the Visceral Bulbo-Spinal Pathway in the Cat and Guinea Pig, J. Comp. Neurol. **42**:393, 1927.

14. Clark, W. E. Le Gros: The Connexions of the Arcuate Nucleus of the Thalamus, Proc. Roy. Soc., London, s.B **123**:166, 1937. See other papers.

15. Walker, A. E.: The Thalamus of the Chimpanzee: IV. Thalamic Projections to the Cerebral Cortex, J. Anat. **73**:37, 1938. See other papers.

16. Bodian, D.: The Projection of the Lateral Geniculate Body on the Cerebral Cortex of the Opossum, Didelphis Virginiana, J. Comp. Neurol. **62**:469, 1935.

17. Poljak, S.: A Contribution to the Cerebral Representation of the Retina, J. Comp. Neurol. **57**:541, 1933.

retrograde cell reaction in newborn and that in adult animals. Presumably, this difference is a regular phenomenon. There are reports in the literature of experiments made with Gudden's method in several parts of the central nervous system. As already noted, mention is often made also of the early disappearance of the cells. Personally, I have seen nearly total loss of cells after eight to ten days in rabbits 10 to 14 days old—for example, in the thalamus after lesions of the cerebral cortex and in the pons and other gray masses in the brain stem with cerebellopetal connections after lesions of the cerebellum. I shall illustrate from two series showing changes in the pons.

Figure 2 represents a transverse section through the pons of an adult rabbit. A limited part of the cerebellum was removed three months before the animal was killed. The figure shows loss of cells in the lateral

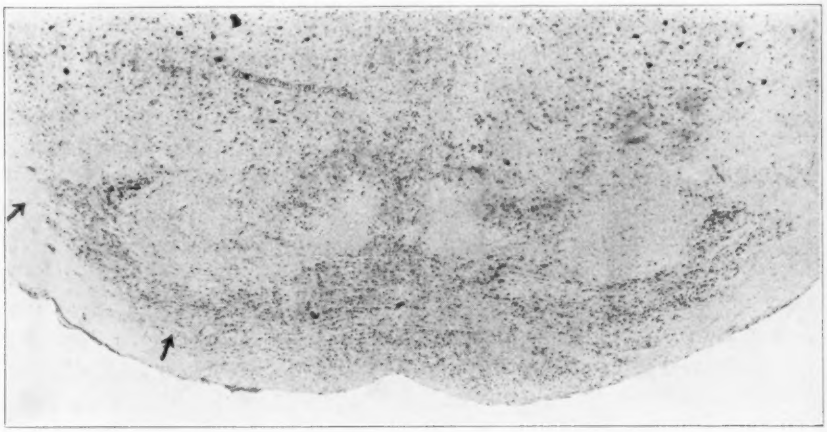

Fig. 2.—Section through the pons of an adult rabbit, three months after extirpation of a limited part of the cerebellum. In the region indicated by arrows, partial loss of cells and atrophy of the remaining cells are seen. Compare with the normal (right) side. Thionine (× 15).

gray matter; the cells lying ventrolateral to the pyramid are reduced in number, and the remainder are decreased in size. This figure should be compared with figure 3, a section through the pons, which approximately was at the same level, from a rabbit 11 days old when operated on and killed eight days later. The cerebellar lesion corresponds almost exactly with that of the animal represented in figure 2. In the same regions of the gray matter of the pons as are shown in figure 2 nearly all the cells have disappeared. It should be pointed out that there is no noticeable difference in the volume of the two halves of the pons.

The observations and the data from the literature indicate that the difference in cellular reaction between newborn and adult animals is a general characteristic feature of the central nervous system.

However, this does not necessarily imply that the method proposed in this paper will be preferable to the others in all cases. As has been shown, the use of young animals has certain drawbacks. Whether these disadvantages are compensated for by advantages in each case will depend on how definite are the results achieved by the other methods. This must be tested in each instance. Generally, however, it can be said that the possibility of securing sufficiently definite changes by the use of the "atrophy method" will be greater the sharper the localization in

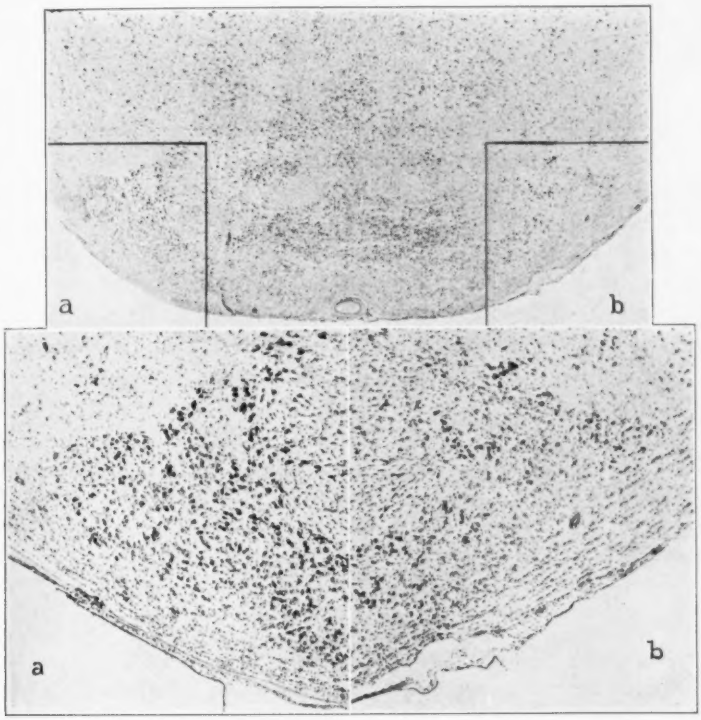

Fig. 3.—Section through the pons of a rabbit 11 days old in which a limited part of the cerebellum (corresponding to that shown in figure 2) was extirpated. The animal was killed eight days later. There was nearly total loss of cells in the lateral gray matter. Thionine (× 15). Below, the normal (*a*) and the affected region (*b*) are shown at higher magnification (× 36).

the projection system, the more uniform the structure of the gray matter, the denser and larger the cells, the smaller the variations in cell size and the larger the proportion which acutely disintegrate. Whether or not artificially shrunken cells appear frequently is also of importance. Further, it must be considered that different types of animals may show variations in the rapidity of the cell changes and that the "newborn type of reaction" may last for different lengths of time after birth in various

types.[18] Likewise, the accompanying glial reaction may vary. The rapidity of myelination will determine how long the cells will lie close together. An important factor will also be whether or not the cells in retrograde reaction in newborn animals differ greatly from the normal cells.

In a given case all these factors will influence the choice of method. Whereas the method proposed here perhaps will not give better results in some structures, e. g., the thalamus, than those obtained by other procedures, it is superior for the inferior olive, and probably also for the pons and several other gray masses. This must, as already stated, be tested in each instance.

SUMMARY

In studying the problem of the olivocerebellar connections, I found none of the usual methods satisfactory. These methods and the results obtained with them are mentioned. On the basis of a systematic experimental investigation of the retrograde cell changes in the olive following lesions of the cerebellum, a modification of the Gudden method has been worked out which gives more definite results: The animals are operated on when 10 to 20 days old and killed after eight to twelve days. This method has the advantage of a practically total loss of the affected cells; at the same time the drawbacks of the original Gudden method are greatly reduced. Advantages and disadvantages of the method are discussed. The results which it yields are demonstrated in the inferior olive and in the pons, and its general applicability is discussed. The method will probably prove satisfactory also in the case of other structures.

18. Individual variations also exist. Newborn animals from different litters are not all of the same size at birth, nor are the animals alike in the same litter. This difference tends to grow more marked during the first days post partum, as the largest animals will often push aside the smaller. It is probable that this difference in bodily development is accompanied by a corresponding difference in the maturity of the central nervous system, which explains the great individual variations in rapidity of the cell changes which are observed.

STUDIES IN MULTIPLE SCLEROSIS

SERUM ENZYMES

CHARLES H. RICHARDS, M.D.
AND
HAROLD G. WOLFF, M.D.
WITH THE TECHNICAL ASSISTANCE OF MARJORIE WINEGARTEN, B.A.
NEW YORK

Theories concerning the cause of multiple sclerosis thus far advanced have failed to withstand experimental investigation or to lead to a suitable diagnostic test. A theory that has recently gained attention is centered about the postulation that an enzyme capable of breaking down myelin is related in some way to the pathologic process. Brickner [1] devised a method to test this concept. He incubated fresh sections of rat spinal cords with blood plasma from patients with multiple sclerosis and from other persons. After suitable staining these sections were compared microscopically. The plasma of both patients with multiple sclerosis and normal subjects proved to have a destructive action on the cord, but Brickner concluded that this action was greater when plasma from the patients was used, and suggested that a lipase was responsible for the destruction.

Weil and Cleveland [2] repeated these experiments and concluded that the deviation from normal was not large enough for any inference to be drawn concerning the importance of lipase in the production of multiple sclerosis. They also found that pancreatic lipase did not produce demyelination of rat spinal cords.

Rivela Greco [3] carried out a similar series of experiments, using serum, plasma and cerebrospinal fluid with the spinal cords of both white rats and rabbits. This author stated that there was no difference

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From the New York Hospital and the Department of Medicine, Cornell University Medical College.

1. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715-726 (April) 1930.

2. Weil, A., and Cleveland, D. A.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375-388 (Feb.) 1932.

3. Rivela Greco, A.: Ricerche col metodo di Brickner sul liquor c. r., sul siero e sul plasma sanguigno di individui affetti da sclerosi multipla e di individui affetti da lesioni epatiche, Note e riv. di psichiat. **64**:1-39, 1935.

in the action of these fluids on the spinal cords whether the subject was normal or had multiple sclerosis.

Weil, Luhan and Balser [4] used a similar histologic technic with concentrated urine and spinal fluid. Substances having a destructive action on myelin sheaths were demonstrated in the concentrated urine from patients with multiple sclerosis, postencephalitic parkinsonism, hepatic disease and pulmonary tuberculosis. Also, the concentrated spinal fluid from patients with various other diseases of the nervous system had a destructive effect on the myelin of the cords.

In a further series of experiments by Brickner,[5] serum and plasma from patients with multiple sclerosis and from normal persons were incubated with an emulsion of egg lecithin under various conditions. The mixtures were then titrated for acid content to determine the amount of hydrolysis of the lecithin during incubation. Brickner claimed that there was a difference in the behavior toward lecithin of serum and plasma from patients with multiple sclerosis and those from normal subjects. Criticism of this work may be stated briefly as follows: (1) The titration values were too small to be of significance. The maximum change in acidity of any preparation over a seventy-two hour period of incubation was about 0.03 cc., an amount near the limit of error of the method used. (2) At the end of twenty-four hours (fig. 1,[5] page 114) the preparations had become more alkaline; so the figures cannot represent the amount of acid split from the lecithin. (3) When the carbon dioxide content was partially controlled by sealing the tubes before incubation, no change in acidity took place (fig. 12, page 126). It is likely, therefore, that the slight variations plotted represent nothing more than changes in the carbon dioxide content of the preparations and experimental error.

In his next paper on this subject, Brickner [6] made use of a method developed by Falk for the identification of enzymes, based on their relative action on a series of esters. However, whereas Falk employed ten esters, Brickner used only three and presented data for only two. The results obtained from patients with multiple sclerosis and from the control subjects were not identical, but nearly so. At most, they suggest a slight difference in behavior of serums from patients with multiple sclerosis and those from normal persons.

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4. Weil, A.; Luhan, J. A., and Balser, B. H.: The Demonstration of Myelolytic Substances in the Urine and Spinal Fluid in Nervous Diseases, Tr. Am. Neurol. A. **61**:142-144, 1935.

5. Brickner, R. M.: Studies of the Pathogenesis of Multiple Sclerosis: II. Evidence of the Presence of an Abnormal Lipase in the Blood in Multiple Sclerosis, Bull. Neurol. Inst. New York **1**:105-135, 1931.

6. Brickner, R. M.: Studies in the Pathogenesis of Multiple Sclerosis: III. Further Evidence of Abnormal Lipolytic Activity in the Blood in Multiple Sclerosis, Bull. Neurol. Inst. New York **2**:119-133, 1932.

Later, Brickner [7] attempted to establish a relationship between the blood esterase and the state of "activity" of multiple sclerosis. Using methyl butyrate as substrate, with and without the addition of quinine (which increases hydrolysis), he concluded that in cases of "active" multiple sclerosis there is low spontaneous esterase activity and in cases of the "inactive" phase high activity. However, the differentiation of high and low esterase activity is based on the effect of the quinine, which, he said, depends on such factors as obesity and certain menstrual influences. If this is true, any differences noted by this method must be influenced by these factors; yet the extent to which they played a role was not indicated in the results presented.

Any demonstrable difference between the blood of a patient with multiple sclerosis and that of another person would be extremely important, but the data already reviewed do not justify claims of a difference in blood enzymes. As already indicated, inspection alone is sufficient to throw doubt on the value of this work. Nevertheless, the theory of abnormal enzyme action in multiple sclerosis seemed worthy of more thorough investigation. Hence, we devised a more accurate method of observing enzyme activity and conducted the experiments to be reported.

METHOD

In this study the esterase and lipase activities of serum have been determined by a manometric method (Rona and Lasnitzki [8]), with use of the ordinary Warburg apparatus. The substrate and the solution of sodium bicarbonate were placed in the vessel proper and the serum in the sack; after equilibration of temperature the serum was mixed with the substrate. As the enzyme of the serum splits fatty acid from the substrate, carbon dioxide is liberated from the solution of sodium bicarbonate, causing an increase in pressure which may be read from the manometer at convenient intervals. Ethyl butyrate and tributyrin were used uniformly throughout, and unless otherwise stated, the terms "esterase" and "lipase" as employed here refer to enzymes acting on these two substrates, respectively. Since the acid is the same in the two substrates, the manometric readings may be converted into terms of cubic centimeters of standard butyric acid by plotting a curve for the carbon dioxide liberated from the mixture by known amounts of the acid. Under the experimental conditions this curve was linear (fig. 1).

The enzymic action of serum on tributyrin is about ten times as great as on ethyl butyrate. Therefore, for convenience a 1:20 dilution of serum was made for the determinations of lipase and a 1:2 dilution for those of esterase, a 0.125 normal solution of sodium bicarbonate being used for the dilution. The length of time finally adopted for incubation was four hours, and the temperature was maintained at 37.5 C. throughout. The substrates were washed with dilute alkali before being used. The diluted serum was saturated with a mixture of 5 per cent

7. Brickner, R. M.: Changes in Blood Esterase Associated with Changes in Activity in Multiple Sclerosis, Bull. Neurol. Inst. New York **4**:656-664, 1936.

8. Rona, P., and Lasnitzki, A.: Eine Methode zur Bestimmung der Lipase in Körperflüssigkeiten und im Gewebe, Biochem. Ztschr. **152**:504-522, 1924.

carbon dioxide and 95 per cent nitrogen before being pipetted into the sack, and the same mixture was passed through the vessels and manometers for one minute before sealing and placing them in the bath.

The blood was taken with sterile precautions; it was allowed to clot and was centrifuged, and the serum was drawn off. About 3 drops of toluene to each 5 cc. of serum was added immediately. This preservative was found not to influence the lipase or esterase activity. In most instances, blood was taken during fasting and the determination made within two or three hours, but if blood had to be taken in the afternoon the serum was stored in the ice box overnight and the determination made the next morning. Such storage was found not to affect enzymic activity.

The determinations were made in triplicate until it was found that the maximum variation was about ± 20 cu. mm. of carbon dioxide over the four hour period. As this maximum variation represents about 0.04 cc. of 0.027 normal (1:400) butyric acid, single determinations were considered satisfactory. However, this variation was frequently rechecked.

Thirty-six different serums were used to establish the relationship between the manometric readings and the acid produced. Readings for all these serums agreed to within ± 20 cu. mm., which is equal to the variation in values for the same serum, as already noted. The relationship was found to be as follows: One hundred cubic millimeters of carbon dioxide was equivalent to 0.190 cc. of 0.027 normal butyric acid for the tributyrin and to 0.197 cc. for the ethyl butyrate, the difference being caused by the difference in serum dilution used with the two substrates.

Acetylcholine hydrobromide [9] was used as a substrate, as well as ethyl butyrate and tributyrin. A 5 per cent solution in distilled water was made fresh each time, for a considerable amount of spontaneous decomposition occurred on standing. The hydrolytic activity of the serum on acetylcholine varied greatly with the concentration of the substrate, so 0.3 cc. of the 5 per cent solution with 1 cc. of a 1:20 dilution of serum was finally adopted as standard in order to make the readings correspond as nearly as possible to those obtained with the other two substrates. The total volume was then made up to 2 cc. by adding 0.7 cc. of a 0.125 normal solution of sodium bicarbonate.

The enzymic action on ethyl butyrate increased with the concentration of substrate up to 0.2 cc., but there was no difference between a concentration of 0.2 and one of 0.3 cc. Therefore, 0.2 cc. was used throughout with 1 cc. of the 1:2 dilution of serum, and the total volume was made up to 2 cc. by adding 0.8 cc. of the solution of sodium bicarbonate. Likewise, 0.1 cc. of tributyrin was found to be sufficient with 1 cc. of a 1:20 dilution of serum, and 0.9 cc. of the sodium bicarbonate solution was added to bring the total volume to 2 cc.

Over the four hour experimental period the amount of carbon dioxide liberated by spontaneous decomposition of the substrate and sodium bicarbonate was from 50 to 60 cu. mm. in the case of both ethyl butyrate and tributyrin, and about 200 cu. mm. in the case of acetylcholine. In the data recorded this amount of spontaneous decomposition was not deducted, as it was constant throughout. The amount of gas liberated from serum without substrate was negligible, being of the order of 5 cu. mm.

In developing this method horse serum was used because it was available in large quantities. It may be noted in passing that horse serum was found to differ from human serum in that it is more active toward ethyl butyrate and

9. Prepared by the Eastman Kodak Co., Rochester, N. Y.

tributyrin, but relatively less active toward acetylcholine. Also, the lipase is much less inactivated by quinine than is the lipase of human serum, although the effect of quinine on the choline esterase is the same in horse and human serum.

RESULTS

In figure 1, curves *A* and *B* show the amounts of carbon dioxide liberated from serum dilutions of 1:2 and 1:20, respectively, by varying amounts of 0.027 normal butyric acid. Over this range the amount of carbon dioxide displaced from solution was directly proportional to the amount of acid used. The other two curves show the average of triplicate determinations of the serum esterase and the serum lipase activity over a period of nine hours. The maximum variation is ± 28 cu. mm. at the end of nine hours. It will be seen that the reaction is linear over this period, and it was found to continue so even up to

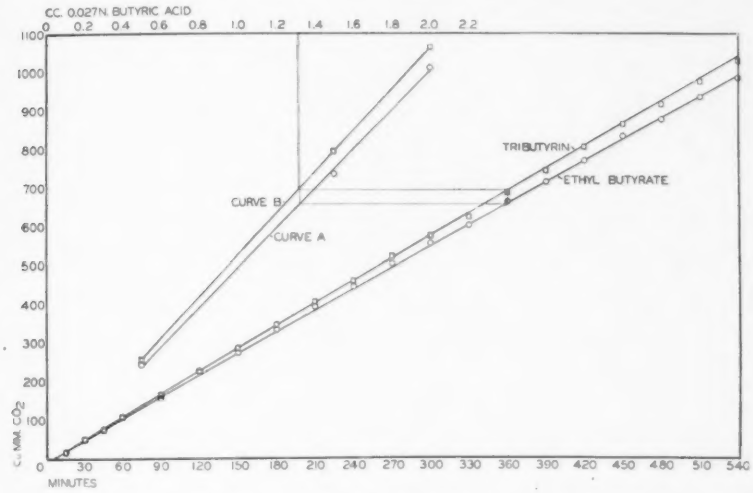

Fig. 1.—Curves *A* and *B* show the number of cubic millimeters of carbon dioxide displaced from 1:2 and 1:20 dilutions of serum, respectively, by varying amounts of butyric acid. The other two curves show the liberation of carbon dioxide due to the hydrolysis of ethyl butyrate with a 1:2 dilution of serum and of tributyrin with a 1:20 dilution over a period of nine hours. The production of acid at any time can be read directly from the graph; e. g., at six hours about 1.32 cc. of 0.027 normal butyric acid was liberated from both preparations. In this figure and in the other figures, circles indicate the values for ethyl butyrate and a 1:2 dilution of serum; rectangles, values for tributyrin and a 1:20 dilution of serum.

sixteen hours. The amount of acid produced at any time can be read directly from the graph; e. g., at six hours about 1.32 cc. of 0.027 normal butyric acid was liberated from each preparation. The curves shown here are taken from an experiment with serum from a patient with multiple sclerosis, but except for the slope, which varies with the individual person, they are typical for human serum whether in health or disease, regardless of its nature.

Twenty-four determinations on 13 normal persons, 78 determinations on 42 patients, selected at random, without evidence of disease of the nervous system and 143 determinations on 30 patients with multiple sclerosis were made. In figure 2 all determinations on each individual subject have been averaged, the amount of carbon dioxide liberated after four hours' incubation being used as the measure of activity. The 13 normal persons and 42 patients without evident disease of the nervous system are grouped together for comparison with the 30 patients with multiple sclerosis. The number of individual subjects represented is too small for detailed comparison, but the curves show the range of variation

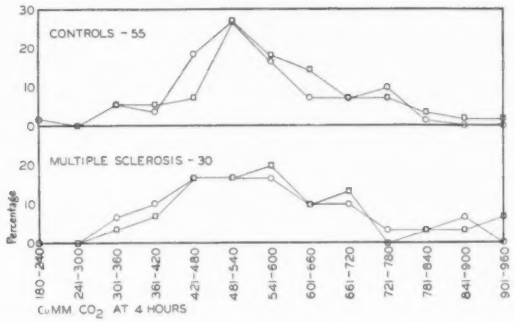

Fig. 2.—Distribution curve for 30 patients with multiple sclerosis and 55 control subjects, calculated on the basis of the cubic millimeters of carbon dioxide liberated at the end of four hours' incubation at 37.5 C.

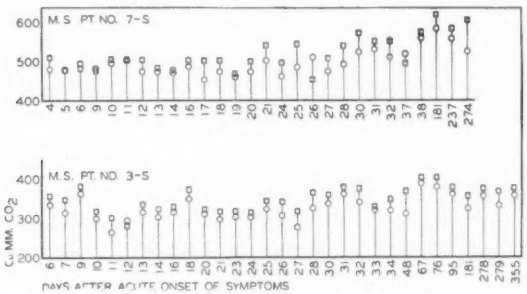

Fig. 3.—Results of 81 determinations of serum esterase and lipase on patients 7-S and 3-S with multiple sclerosis, on various days following an acute exacerbation of the disease in each patient. The values plotted are the cubic millimeters of carbon dioxide liberated after four hours' incubation at 37.5 C.

in esterase and lipase activity, and the essential similarity in this range in patients with multiple sclerosis in the control subjects. The lowest values are found in debilitated patients, apparently regardless of the cause of debilitation (Milhorat [10]).

Figure 3 shows the results of a series of observations on 2 patients with multiple sclerosis (cases 3-S and 7-S). Patient 3-S came to the hospital with

10. Milhorat, A. T.: The Choline-Esterase Activity of the Blood Serum in Disease, J. Clin. Investigation **17**:649-657, 1938.

an acute exacerbation of multiple sclerosis, with nystagmus, slurred speech, hyperactive deep reflexes, vomiting, low blood pressure and other signs of shock. She improved rapidly up to the sixth day, when the first determinations of esterase and lipase were made. On the seventh day there was another acute exacerbation of symptoms. After this her recovery was slow, but there were no further crises. The chart shows the values for esterase and lipase on various days following the first acute episode up to nearly one year later, when her clinical condition was almost normal. The variation is not greater than that seen in normal persons, despite the great clinical change over this period.

The upper graph shows the results of similar determinations on patient 7-S throughout recovery following an acute onset of symptoms.

In figure 4 are shown the averages for esterase and lipase activity for each of the 30 patients with multiple sclerosis. First to be noted is the wide variation in liberation of carbon dioxide among individual patients (see figure 2 for the distribution curve), from about 300 to 900 cu. mm. during four hours of incubation. The second fact apparent from the chart is that the values for esterase and lipase vary together, and this is true of those for choline esterase, although this is not shown.

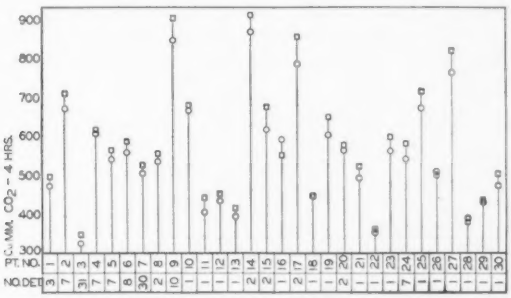

Fig. 4.—Values for serum esterase and lipase activity in each of the 30 patients with multiple sclerosis studied. Where more than one determination was made on a patient, the values were averaged and the number of determinations is shown in the column *No. Det.* The patient's number is given in column *Pt. No.*

Certain agents known to influence enzyme action were used in an effort to determine whether serums of patients with multiple sclerosis can be differentiated from serums of other persons by a difference in the effect of these agents. The results are briefly presented.

Quinine.—Some of the results with quinine are shown in figure 5. This substance enhanced the action of serum on ethyl butyrate and depressed its action on both tributyrin and acetylcholine. These effects were more pronounced with increasing concentration, up to 0.2 cc. of a 0.2 per cent solution in 2 cc. of mixture (1:5,000 dilution). But 0.2 cc. of a 5 per cent solution slightly depressed the esterase also. This action of quinine on serum from patients with multiple sclerosis was identical with that on other serums.

Potassium Cyanide.—In a concentration of 0.2 cc. of a 5 per cent solution in 2 cc. of mixture, potassium cyanide had no appreciable effect on the esterase, lipase or choline esterase activity of patients with multiple sclerosis or of other persons. There may have been a tendency to activate the lipase to a slight extent, and lipase of heated serum was slightly activated.

Hydroquinone.—Two-tenths cubic centimeter of a 0.2 per cent solution in 2 cc. of mixture inhibited the lipase and choline esterase to about 50 per cent activity, while 0.2 cc. of a 0.02 per cent solution inhibited the lipase and choline esterase to about 80 per cent activity and did not affect the esterase. These effects were the same in serums from patients with multiple sclerosis and in those from control subjects.

Physostigmine.—Two-tenths cubic centimeter of a 0.013 per cent solution inhibited all the enzymes to about 15 or 20 per cent activity, although there was slightly less inhibition of the choline esterase. The serums of both patients with multiple sclerosis and normal persons were similarly affected.

Prostigmine.—Two-tenths cubic centimeter of a 1:10 solution[11] inhibited activity of esterase and lipase to about 50 per cent, both in serums from patients with multiple sclerosis and in those from control subjects.

Heat.—Heating for fifteen minutes at 55 C. inhibited activity of esterase and lipase to about 75 per cent, and heating for one-half hour at 60 C. completely

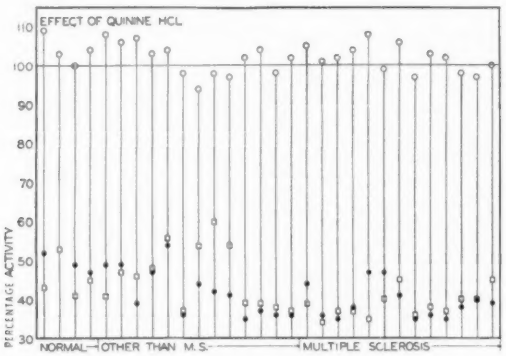

Fig. 5.—The effects of quinine hydrochloride in vitro on the activity of serum toward ethyl butyrate, tributyrin and acetylcholine are plotted as percentages of activity when the quinine is not present. The concentration of quinine in each instance was 0.2 cc. of a 0.2 per cent solution in a total volume of 2 cc. The results shown are for normal subjects, patients with multiple sclerosis and other patients, as indicated. In this figure, values for acetylcholine are indicated by solid circles.

inactivated both enzymes. Heat had no differential action on serum from patients with multiple sclerosis.

Compound Solution of Iodine.—It was found that compound solution of iodine and serum together with a solution of sodium bicarbonate gave an evolution of gas without the presence of any substrate. Further, more gas was liberated from the serum of a 1:20 dilution than from the more concentrated (1:2) serum. With a 1:100 dilution of the serum again less gas was produced. Boiling the serum had the peculiar effect of decreasing the amount of gas liberated from the 1:2 dilution of serum and increasing still more the amount from the 1:20 dilution, without affecting the amount from the 1:100 dilution. The foregoing results were true both of serums from patients with multiple sclerosis and of those from control subjects, and have not yet been satisfactorily explained.

11. Manufactured by Hoffmann-La Roche, Inc., Nutley, N. J.

Various other substances have been used in an effort to find one which would serve to distinguish serum of a patient with multiple sclerosis from that of any other person. These agents were morphine, yohimbine, atropine, guanidine, ascorbic acid, alcohol, chloroform, hexylresorcinol, and inorganic salts, such as magnesium carbonate, potassium permanganate and lead acetate. While some of these substances did have an inhibiting effect on one or more of the enzymes studied, no differential action could be noted which would distinguish serum of patients with multiple sclerosis from that of any other person.

Various other substrates have been used, including an emulsion of egg lecithin similar to that employed by Brickner. Simpler esters and glycerides, in addition to those discussed, were employed. The results of these determinations are indicated briefly.

Lecithin.—Both commercial egg lecithin [12] and the phosphatide fraction of fresh extracts of human brain have repeatedly been used as substrates, but with our method it has been impossible to demonstrate any hydrolytic activity. Neither has it been possible to find any substance which would increase any slight action and so make it measurable. Serum and lecithin were incubated together, and the inorganic phosphorus was ascertained before and after incubation as an index of hydrolytic activity of serum toward this substrate. There was little or no increase in inorganic phosphorus during such incubation, and certainly no indication of any difference between the serum of persons with multiple sclerosis and that of other persons.

Other Lipoid Fractions.—Other fractions of fresh brain extracts used were partially purified cerebrosides and sphingomyelin, as well as the crude total ether extract, but no activity toward these as substrates could be detected by our method with serums either from normal subjects or from patients with multiple sclerosis. However, further studies on these substrates are under way.

Other simple substrates were tested. Ethyl acetate, ethyl acetoacetate, tricaprylin, triacetate, monobutyrin and phenyl acetate all showed some hydrolysis by this method, but it was not possible to detect any significant difference between the activity of serum from patients with multiple sclerosis and that of serum from other persons.

COMMENT

From the data presented, it is evident that there is considerable variation in the level of the serum esterase, lipase and choline esterase. There is, however, only slight variation in any one person's level over long periods (eleven and a half months). Enzymic activity of males tends to be higher than that of females. If the action of one enzyme is high, that of the others is usually high also. Debilitation, apparently from any cause, greatly lowers the activity toward all three substrates.

Quinine is the only substance so far discovered which shows a marked differential effect on the activity of these three enzymes, by activating the ethyl butyrase and depressing both the tributyrinase and the choline esterase. It is interesting to note that in this respect, as well as in the effect of hydroquinone, the choline esterase behaves more like the lipase than like the ethyl butyrase.

12. Prepared by Eimer & Amend, New York.

The failure to obtain any evidence of enzymic action on the more complicated substrates, such as lecithin and emulsions of brain fat, may mean that there is no enzyme in serum capable of attacking these substances, but these experiments do not justify such a conclusion. It is possible that such an enzyme or enzymes may be present in too small concentration to be detected by the method here employed. The method limits the p_H of the mixture to the alkaline side, and the optimum p_H of serum enzymes capable of hydrolyzing lecithin has not been determined. Also, since these substances contain the higher fatty acids, the increase in acidity due to their hydrolysis may be too slight to displace a measurable amount of carbon dioxide from solution. Many of these fats contain bases, such as choline, and other radicals; as there is no way of knowing a priori where an enzyme will attack such a complicated molecule, it would be necessary to check all possible products of hydrolysis before concluding that no action has taken place.

In considering the theory that abnormal enzymic activity plays an etiologic role in multiple sclerosis, it should be kept in mind that one of the most characteristic features of an enzyme is its specificity; in view of the fact that the myelin is the substance attacked in this pathologic process, it follows that myelin should be the substrate in any experiments designed to test this theory. Practically, this is difficult, for there is no adequate method of measuring the hydrolysis of such a complicated substance. Also, it is at least theoretically possible that disorganization of the physical structure alone, without any chemical change, would be enough to initiate disintegration of the myelin.

For the foregoing reasons, the experiments reported here are not considered as having disproved the theory that an abnormal enzyme may be involved in the pathogenesis of multiple sclerosis. However, contrary to Brickner's findings, they do show beyond doubt that the action on these simple substrates of serum from patients with multiple sclerosis does not differ from that of normal serum.

SUMMARY

A manometric method is described which is more accurate and convenient than titration for determining the esterase, lipase and choline esterase activity of serum. The activity of these enzymes has been ascertained in normal persons, patients with multiple sclerosis and other patients, ethyl butyrate, tributyrin and acetylcholine being used as substrates.

Individual levels of activity are maintained nearly constant over long periods. Debilitation causes a pronounced lowering of activity of all these enzymes.

Quinine hydrochloride in vitro activates slightly the esterase, but inactivates the lipase and choline esterase of serum whether from patients with multiple sclerosis or from normal subjects.

No evidence of hydrolytic activity of any serum toward lecithin or various emulsions of brain fat has been demonstrated by this method.

No difference has been found in the behavior of serum from patients with multiple sclerosis and serum from any other persons. Moreover, no change in the activity of these enzymes has been demonstrated during remission or exacerbation of the signs and symptoms of multiple sclerosis.

EFFECT OF PHENOBARBITAL ON THE MENTALITY OF EPILEPTIC PATIENTS

ESTHER SOMERFELD-ZISKIND, M.D.
AND
EUGENE ZISKIND, M.D.*
LOS ANGELES

Phenobarbital is probably at present the most widely used medicinal agent in the treatment of convulsive states. Inasmuch as its action is merely palliative, treatment is often prolonged or continued indefinitely. An inadequate dose is usually prescribed by the general practitioner, as he fears toxic effects. Therefore phenobarbital is frequently in disrepute with the patient before he comes to the specialist. Textbooks also are conservative with regard to this drug. Though the virtues of phenobarbital are admitted, the hazards are too often overemphasized.

In our experience in 600 cases of convulsive states, large doses of phenobarbital have often been necessary to keep patients free from seizures. Yet we have never encountered an instance of serious idiosyncrasy to the drug. Mental deterioration does occur in a variable percentage of epileptic patients,[1] and it is conceivable that chronic intoxi-

* From the Department of Medicine (Neurology), the University of Southern California School of Medicine.

1.(*a*) Wallin, J. E. W.: Experimental Studies of Mental Defectives: A Critique of the Binet-Simon Tests and a Contribution to the Psychology of Epilepsy, Educational Psychology Monograph 7, Baltimore, Warwick & York, Inc., 1912. (*b*) Yawger, N. S.: The Mental Manifestations of Epilepsy, J. Abnorm. Psychol. **7**:420 (Feb.-March) 1913. (*c*) Fox, J. T.: The Response of Epileptic Children to Mental and Educational Tests, Brit. J. M. Psychol. **4**:235 (Nov.) 1924. (*d*) Cookson, S. H.: An Analysis of One Hundred Cases of Fits in Children, Arch. Dis. Childhood **2**:178 (June) 1927. (*e*) Ninde, F. W.: The Application of the Auditory Memory Span Test to Two Thousand Institutionalized Epileptics: A Study in Relative Associability, Westchester, Pa., The Temple Press, 1927. (*f*) Dawson, S., and Conn, J. C. M.: The Intelligence of Epileptic Children, Arch. Dis. Childhood **4**:142 (June) 1929. (*g*) Patterson, H. A., and Fonner, D.: Some Observations on the Intelligence Quotient in Epileptics: Preliminary Report, Psychiatric Quart. **2**:542 (Oct.) 1928. (*h*) Paskind, H. A.: Extramural Patients with Epilepsy with Special Reference to the Frequent Absence of Deterioration, Arch. Neurol. & Psychiat. **28**:370 (Aug.) 1932. (*i*) Allan, S. M.: Ketogenic Diet in Epilepsy, J. Ment. Sc. **79**:677 (Oct.) 1933. (*k*) Bridge, E. M.: Mental State of the Epileptic Patient, Arch. Neurol.

cation with drugs may be partly responsible for intellectual impairment in some patients treated for convulsions. However, most of the pertinent statements in the literature are conjectural.

Grinker [2] reported general improvement in the mentality of epileptic patients taking phenobarbital. This was noted both in defective persons and in those of normal intelligence. After the seizures were inhibited by the medicine, patients became more animated in conversation and more active physically. We decided to subject the matter to investigation, since we could discover no controlled study as to the effect of phenobarbital on the sensorium.

METHOD

Cases and Situation.—One hundred cases of convulsions comprise the present study. The patients were attending the outpatient departments of the Los Angeles County General and Cedars of Lebanon Hospitals. As a group, the attacks were moderately frequent before the patients came under our care, the grand mal seizures averaging four a month and the petit mal twenty. They represent virtually untreated patients, even though the average duration of illness was six years. Ninety-six per cent of the patients had had at least one grand mal attack; 37 per cent had both grand and petit mal seizures; 37, grand mal seizures alone; 2, petit mal seizures alone; 5, jacksonian spells; 5, myoclonic twitches; 2, rages; 2, automatisms; 1, dreamy states, and 1 per cent, amnesic attacks.

The chronologic ages ranged from 3 to 58 years, the mean being 26 years. The median mental ages obtained with five different psychologic tests ranged from 3 to 16 years, the mean being 13 years. As in most studies on epileptic persons, males were in preponderance—66 per cent.

"Symptomatic" as well as idiopathic forms of the disease were included because we desired to study a cross section of cases of convulsive states, and no fundamental difference exists between the convulsions of known and those of unknown origin. In 91 per cent of the cases there were abnormal neurologic findings, but many of these were minor, such as slight facial asymmetries of questionable significance. In 43 of the cases the etiologic factor was uncovered, but in 57 it was not. The cases in which the cause was known were distributed as follows: trauma, 12 cases; syphilis, 7; alcoholism, 6; otitic, typhoid or measles meningoencephalitis, 6; tumor of the brain, 4; psychogenic or hysterical disorders, 3; organic lesions, not otherwise differentiated, 2; familial myoclonus, 1; Kowjene-

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& Psychiat. **32**:723 (Oct.) 1934. (*l*) Fetterman, J., and Barnes, M. R.: Serial Studies of the Intelligence of Patients with Epilepsy, ibid. **32**:797 (Oct.) 1934. (*m*) Rosanoff, A. J.; Handy, L. M., and Rosanoff, I. A.: Etiology of Epilepsy, with Special Reference to Its Occurrence in Twins, ibid. **31**:1165 (June) 1934. (*n*) Sullivan, E. B., and Gahagan, L.: On Intelligence of Epileptic Children, Genetic Psychology Monograph, Provincetown, Mass., Journal Press, October 1935, vol. 17, no. 5. (*o*) Collins, A. L.; Atwell, C. R., and Moore, M.: Stanford-Binet Response Patterns in Epileptics, Am. J. Orthopsychiat. **8**:51 (Jan.) 1938.

2. Grinker, R. R.: The Proper Use of Phenobarbital in the Treatment of the Epilepsies, J. A. M. A. **93**:1218 (Oct. 19) 1929.

3. Footnote deleted by the authors.

kow's syndrome (epilepsia partialis continua), 1, and hypothyroidism, 1. The cases of hysterical type were included inadvertently and were discarded in the final tabulations.

Medical Examination.—Each patient was thoroughly studied from the medical standpoint at the outset. Interns secured a complete anamnesis, including a detailed account of the seizures and the family background. A special questionnaire covered the histories of birth and development, all past illnesses associated with spasms, delirium or unconsciousness and any relevant trauma. Whenever possible, the mother was brought into the clinic to answer the questions in person, but if she was living out of town the blank was mailed to her with the request that a local physician fill it out. In addition, a description of the attacks was obtained from a friend or relative who had observed one or more. The patient then received general physical and neurologic examinations. Routine laboratory examinations included urinalysis, a complete blood count, a Wassermann test of the blood, a roentgenogram of the skull, and determinations of the pressure, cell count, globulin content and Wassermann and colloidal gold reactions of the spinal fluid. After these, the patient underwent a thirty-six hour fast to exclude hypoglycemia as a causative factor of the seizures. Pneumoencephalographic studies, perimetry, vestibular tests, psychiatric examination or personality studies were added when needed.

Psychologic Tests.—The purpose was to compare the mentality of epileptic patients before and after phenobarbital medication. All psychologic testing was done individually by one of us (E. S. Z.), without assistance, to secure uniformity of method. No patient was given the psychologic examination until after the medical tests. The first patient was examined on Feb. 5, 1934.

The battery of tests [4] consisted of the Stanford-Binet, the Goodenough drawing of a man, the Healy-Fernald construction puzzle A, the Knox cube and the Woodworth-Wells easy directions tests, as well as a free association experiment. Standard procedure was used incidental to the Goodenough,[5] the Stanford-Binet [6] and the Healy-Fernald [7] tests. The Goodenough drawing measures motor ability and gives an inkling of the patient's concept of the entity man. The puzzle "brings out perception of relationships of form and also the individual's method of mental procedure for the given task, particularly his ability to profit by the experience of repeated trials, in contradistinction to the peculiar repetition of impossibilities characteristic of the subnormal and feeble-minded groups."[7a] The Knox cube test [8] was performed according to Pintner's modification.[9] It demands

4. Dr. Ellen B. Sullivan, of the department of psychology, the University of California at Los Angeles, advised us as to selection of tests and statistical methods.

5. Goodenough, F. L.: Measurement of Intelligence by Drawings, Chicago, World Book Company, 1926.

6. Terman, L. M.: The Measurement of Intelligence, Boston, Houghton Mifflin Company, 1916.

7. (*a*) Healy, W., and Fernald, G. M.: Tests for Practical Mental Classification, Psychological Monographs, whole no. 54, Princeton, N. J., Psychological Review Company, 1911, vol. 13, no. 14. (*b*) Pintner, R., and Paterson, D. G.: A Scale of Performance Tests, New York, D. Appleton and Company, 1921.

8. Knox, H. A.: A Scale Based on the Work at Ellis Island, for Estimating Mental Defect, J. A. M. A. **62**:741 (March 7) 1914.

9. Pintner, R.: The Standardization of Knox's Cube Test, Psychol. Rev. **22**: 377, 1915.

good attention, memory, mental organization, orientation and ability with number patterns. Of the two forms of the Woodworth-Wells easy directions test,[10] we used the second throughout. For the free association experiment, groups of 25 words were taken from the Kent-Rosanoff[11] list of 100 words. At each sitting a different group of 25 words was employed. It has been shown[10] that lists of 10 and 20 words give general tendencies similar to those of long lists for free association; hence we felt justified in using 25 instead of 100 words to save time. Both the first response word and the reaction time were recorded. The procedure was otherwise as indicated by Wells.[12] The normal mean value for association time may be taken as 2 seconds.[12] Jung[13] cited a value of 1.8 seconds. Crosland,[14] in six experiments on 45 university students, found that the mean reaction time ranged from 1.4 to 2.2 seconds.

Each battery of tests took about two hours, requiring two sessions more often than one. If the latter was feasible, a rest of at least ten minutes was given at the end of the first hour. Every test in the battery was not applicable in all cases, as youth, illiteracy, language difficulty or a physical handicap sometimes interfered.

When the psychologic tests were completed, treatment for the seizures was prescribed.

Control Subjects.—Alternate patients, in the order of observation, were given phenobarbital, and the others were used as controls. There were a few unavoidable deviations. For instance, a patient with severe epilepsy might refuse to continue to attend the dispensary unless given a sedative. If anything, these exceptions weighted the series against the favorable outcome of our thesis. Most of the controls were placed on a ketogenic or dehydration regimen, to which, for lack of urging or financial assistance, they rarely conformed. Thus, the controls were equivalent to untreated patients. Two syphilitic patients in the control group received antisyphilitic therapy, but they were followed through a second year with the same therapy plus phenobarbital.

Thirteen patients were used as controls the first year and were given phenobarbital the second year. We consider the comparative data for these subjects as the most significant.

The phenobarbital group of patients took daily from one to three doses of the medicament in tablet form for one year. No patient was included for the annual retest unless the phenobarbital had been taken at least once a day for not less than ten continuous months immediately prior to the time of retesting. The average total daily dose ranged from ¾ grain (0.05 Gm.) to 4½ grains (0.3 Gm.), the mean being 2¾ grains (0.2 Gm.). The most frequent dose was 1½ grains (0.1 Gm.) before breakfast and again at bedtime.

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10. Woodworth, R. S., and Wells, F. L.: Association Tests, Psychological Monographs, whole no. 57, Princeton, N. J., Psychological Review Company, December 1911, vol. 13, no. 5, p. 78.

11. Kent, G. H., and Rosanoff, A. J.: A Study of Association in Insanity, Am. J. Insan. **68**:37, 1920.

12. Wells, F. L.: Mental Tests in Clinical Practice, Yonkers-on-Hudson, N. Y., World Book Company, 1927.

13. Jung, C. G.: Studies in Word-Association, London, William Heinemann, 1918.

14. Crosland, H. R.: The Psychological Methods of Word-Association and Reaction-Time as Tests of Deception, University of Oregon Publication, Eugene, Ore., University of Oregon Press, January 1929, vol. 1, no. 1.

There were 48 patients in the phenobarbital group and 42 in the control group. They were comparable as to age, sex, intelligence and duration of seizures. As to frequency of spells, the phenobarbital group was more heavily burdened (table 1) in that the average number of convulsions was four each month, as compared with three for the controls. The additional patients in the phenobarbital group came from those who served as controls the first year but were treated the second. Twenty-three patients were not given the annual examination—2 had surgical intervention; 7 disappeared, and 14 failed to adhere to a single type of schedule throughout a year.

To determine the early effect of the phenobarbital, about one month after the institution of treatment a small battery of retests was performed, consisting of the easy directions and Knox cube tests and a second set of 25 words for free association. One year subsequent to the beginning of therapy the original battery of six tests was repeated; a third set of association words was used.

TABLE 1.—*Comparison of Incidence of Seizures Before and After One Year of Treatment*

	Control Patients (42)				Phenobarbital Patients (48)			
	Percentage Having This Type of Spell		Average Number of Spells Each Month		Percentage Having This Type of Spell		Average Number of Spells Each Month	
Type of Spell	Before Treatment Period*	After 1 Year	Before Treatment Period*	After 1 Year	Before Treat-ment	After 1 Year	Before Treat-ment	After 1 Year
Grand mal	93	91	8	2	96	75	4	0.5
Petit mal	45	45	11	4	48	44	24	3
Jacksonian	4	2	..	..	4	2		
Myoclonic twitching	4	4	..	..	8	4		
Automatisms	..	..	..	..	4	4		
Dreamy states	2	2						
Rages	2	..	..	..	..	2		
No spells	..	9	..	..	..	25		

* The control patients received no treatment.

During the trial year the patients returned every two months for observation or treatment, at which times we discussed and filed the records of all spells kept by the patient and relatives.

Seven patients were tested before and after two years of treatment with phenobarbital.

RESULTS

Comparison After One Month.—After one month of treatment, there were only slight and insignificant psychologic differences between the two groups and between the initial and the present ratings in the Knox cube, Woodworth-Wells easy directions and association tests.

Comparison After One Year.—After one year of treatment, the phenobarbital group compared favorably with the controls. The average intelligence quotient and the mental age for each group were essentially the same as they had been the year before.[15] A special tabulation was made of the changes in mental

15. Fifty large tabulations were set up in order to arrive at the conclusions mentioned in the present paper, but we decided not to burden the reader with them. However, we will send copies to any one interested. The figures mentioned are averages, around which there is the expected variability.

age in the patients less than 16 years old, that is, those whose mental age was expected to increase. The control group gained the normal 12 months in mental age in the test year, whereas 11 children treated with phenobarbital obtained more than their normal increment of intellectual development in that the mental ages increased on an average of 16 months in the test year.

Both the control and the phenobarbital series after one year yielded improved scores in the Goodenough drawing of a man and the Healy-Fernald construction puzzle. A practice effect is surmised. The Knox cube scores remained stationary. In the easy directions test a slight increase in the number of errors was noted for the controls, but for the treated groups the number of errors remained constant.

TABLE 2.—*Effect of Large Doses of Phenobarbital*

Case No.	Average Daily Amount of Phenobarbital Taken for 1 Yr., Grains	Intelligence Quotient Before Treatment	Intelligence Quotient After 1 Year of Treatment
13	3.1	69	74
17	3.0	117	107
20	3.0	77	88
25	3.0	113	107
27	3.0	98	108
32	3.0	128	123
37	3.9	94	83
38	3.0	81	88
40	3.6	80	83
51	3.0	104	99
57	3.0	96	97
65	4.5	101	96
66	3.3	107	101
71	3.9	70	74
74	3.0	80	82
79	3.2	93	87
80	3.8	93	87
85	3.0	64	66
90	3.4	84	82
92	3.0	94	96
96	3.7	84	90
99	3.0	104	116
Number of cases		22	
Range of dose		3.0 to 4.5 grains (0.2 to 0.3 Gm.) daily	
Average dose		3.3 grains (0.2 Gm.) daily	
Initial intelligence quotient			
Range		64 to 128	
Average		92	
Intelligence quotient after 1 year of phenobarbital treatment			
Range		66 to 123	
Average		92	

Free association showed a similar trend. In the control group the average reaction time dropped from 2.8 to 2.7 seconds, but in the phenobarbital group the average was still 2.9 seconds. The mean number of individual (abnormal) responses initially was two in the treated group and one in the control group. After one year of treatment it was one in both groups. These differences are not particularly significant.

The changes in intelligence quotients were computed for 22 patients receiving higher doses of phenobarbital than the others, the amounts ranging from 3 to 4.5 grains (0.2 to 0.3 Gm.) daily, the average daily dose for the whole year for this group being 3.3 grains (0.2 Gm.). There was no perceptible difference in intelligence at the beginning and at the end of the year.

Table 1 reveals that the phenobarbital group originally had a burden of convulsions 27 per cent greater than did the controls, but that at the end of the test year the treated group had only 20 per cent as many convulsions as did the controls and 75 per cent as many petit mal attacks. During the year of phenobarbital treatment, 25 per cent of 48 patients had no spells of any kind; 54 per cent had fewer grand mal seizures than in the previous year, and 13 per cent showed a decreased number of minor spells. In all, 79 per cent of the patients given phenobarbital for a year were either free from spells or definitely improved. Sullivan and Gahagan,[1n] in their careful study, found no positive correlation between frequency of spells and mental changes.

Comparison After Two Years.—Seven patients were tested before and after two years of medication. At the second test improvement was noted on the average in every item of the battery, except that in the Woodworth-Wells performance the number of errors remained stationary and in free association tests the number of "individual" responses rose from none to one. In 4 cases the mean reaction time to 100 stimulus words after two years of phenobarbital treatment was 2.2 seconds. This is normal. On the whole, the slight changes after two years of treatment were in the direction of normality.

Comparison of Control and Treatment Years for the Same Patients.—In 13 cases the first year was used as a control, and phenobarbital was given throughout the second year. The Stanford-Binet mental ages and intelligence quotients were stationary during the two years, averaging 15 years and 100 respectively. In the rest of the battery there was progressive improvement from the initial to the annual and second annual tests, except that in the Knox cube test the score did not change. In free association tests the mean reaction time was at first 2.8 seconds; it remained the same after the control year and decreased to 2.5 seconds at the end of the year of phenobarbital therapy.

General Psychologic Data.—Before treatment the intelligence quotients in the series as a whole ranged from 39 to 153, the mean being 93. Other remarks in the present section refer only to the first 75 cases.[16]

The percentages of success and failure in individual items in the Stanford-Binet setup ranged from 49 to 81 per cent. Normal persons show the same distribution. In order to determine whether there were any special intellectual aptitudes or disabilities in epileptic persons, we classified the various Stanford-Binet items as to traits represented;[6] then we computed the percentages of patients passing the tests above their mental age and of those failing at or below their mental age. Normal variations were secured for abstraction, associative processes, comprehension, discrimination, generalization, manipulation of mental imagery, maturity of apperception and spontaneous interest in the world about them. In 47 per cent of the memory items in the Stanford-Binet test the patients failed, as they did also in 36 per cent of items taxing attention. On the other hand, 36 per cent of patients were above their mental age in memory ability. In acquisition and use of language 36 per cent tested below their mental level.

Only 2 of 97 epileptic patients failed to solve the Healy-Fernald construction puzzle A in the time allotted. Learning curves were devised for the mean first, second and third trials on the puzzle. One curve was for the time taken to solve

16. The first 75 cases of the series were the subjects of a thesis presented by one of us (E. S. Z.) to the faculty of the department of psychology, the University of California at Los Angeles, in partial fulfilment of the requirements for the degree of Master of Arts, in June 1935.

it, and the other was for the number of moves necessary. Both learning curves were normal.

Comparison of the mental ages in the Goodenough and the Stanford-Binet test reveals consistently poorer success in the former. The mean mental age for the drawing test was 12 years for each chronologic decade from 10 to 50 years. Below 10 and above 50 years, of course, the scores decreased considerably. High drawing ability did not show a positive correlation with high mentality. The mean and median mental age scores on the Knox cube test, 12 and 10 years, respectively, were also below the expectations aroused by the intelligence quotients.

For 62 patients not under treatment, the reaction times in the free association experiment were measured to tenths of a second, at 113 sessions of 25 words each, giving a total 2,825 word reactions. The range of reaction times was from 0.7 to 23.2 seconds, the mean being 2.8 seconds. This indicates a slower reaction time in epileptic persons, with greater variability, than in well persons. The range of percentages of "individual" responses was somewhat wide, from 0 to 56, but the mean was normal, being 3.

Comparison of Cases of Symptomatic and of Idiopathic Epilepsy.—Of the first 71 cases there were 41 of idiopathic as compared with 30 of symptomatic type. The mean intelligence quotient for the patients with idiopathic epilepsy was 97, but for those with the symptomatic type it was only 88. The chronologic ages of the two groups were similar; yet the median mental ages for the entire battery of tests presented a higher mean in the idiopathic than in the symptomatic group—14 and 12 years, respectively. This difference is not unexpected, since the groups for which no cause is established, the "idiopathic," obviously do not have such extensive damage to the brain as the others.

COMMENT

Other Possible Causes of Mental Deterioration.—Mental impairment in epilepsy may be ascribed to causes other than possible chronic poisoning from drugs. In considering such factors we would include: (1) the etiologic agent for the seizures, (2) the altered physiologic state during seizures and (3) accidental trauma during spells.

1. Deterioration may be incident to the etiologic agent for the convulsions. Brain tissue necessary for normal intelligence may be involved by the same factor that causes seizures and still be independent of the fits. Whether the mental defect precedes, coincides with or follows the onset of convulsions depends on the primary localization and extension of the pathologic process. In many cases the intellectual defect precedes the appearance of epilepsy by years. In fact, convulsive episodes occur in most types of mental deficiency dependent on a gross cerebral lesion. Any generalized pathologic element, whether infectious, neoplastic, toxic or traumatic, can conceivably affect various neural patterns. This relationship is relatively clear for demonstrable lesions but, though not as apparent, it probably holds for the cryptogenic types of epilepsy also. In epilepsy of hypoglycemic origin, in which the drop in blood sugar induces seizures, mental symptoms may precede the convulsions by a few minutes to several hours. Such repeated attacks

will presumably impair cerebral function by destruction of tissue. A similar sequence of events is expected in convulsions consequent to cerebral anemia from heart disease. This sequence is manifest also in other pathologic cerebral states.

2. Intellectual changes may be due to the convulsions themselves and result from an altered physiologic state at the time. During spells of unconsciousness lasting several minutes, cerebral anemia or anoxemia could destroy the delicate cortical cells, as could also the venous engorgement and capillary hemorrhages. It is known that intracranial pressure is increased during seizures. However, it may be that these features result from the underlying pathologic state rather than from the convulsions themselves.

3. Repeated cerebral concussion sustained in injuries of the head during fits may contribute to mental deterioration in epileptic persons. This is most likely to occur when aura is absent.

Data on Intelligence.—It is difficult to find exact measurements of reaction time in the literature on epilepsy. Jung [13] mentioned prolongation of reaction time in several cases. Kent and Rosanoff [11] obtained with normal persons an average of 7 per cent of individualistic responses in the free association experiment, the range being from 0 to 42 per cent. These authors also examined 24 institutionalized epileptic persons,[17] who exhibited a greater number of "individual" responses than do normal persons. No statistics were given in regard to this phase. The patients with seizures tended to repeat the same word many times and to use nonspecific reactions. Jung's convulsive patients often replied with predicates and egocentric words. In our series of patients there was nothing in the response words to differentiate them from normal.

The absence of any marked deviation in the intelligence of noninstitutionalized epileptic patients is in line with recent opinion. Institutional patients show a greater degree of mental impairment, because patients with recurrent convulsions are not as a rule committed to epileptic colonies unless they are defective. The worst types, those not responding to treatment, soon fail to maintain contact with the clinic.

Significance of Results.—Our results indicate that the physician need not hesitate to prescribe phenobarbital in doses of 1½ grains (0.1 Gm.) two or three times daily for protracted periods. A slight rash may occasionally be encountered at the beginning of a course of therapy, but almost always, if treatment is interrupted for a short period and phenobarbital is then resumed in smaller doses, a satisfactory increase to effective amounts can gradually be accomplished. Arthritic symptoms are an occasional manifestation after prolonged treatment. They are an indication for reduction of the dose. As already stated, we have

17. Kent, C. H., and Rosanoff, A. J.: A Study of Association in Insanity, Am. J. Insan. **68**:390, 1910.

not encountered a serious idiosyncrasy to phenobarbital in an experience with 600 cases of convulsive states.

We must admit that many years of sedation might affect mentation, even though treatment for a year or two did not. Paskind [18] judged deterioration by comparing the occupations of patients before and after their taking bromides in amounts sufficient to reduce seizures markedly from one to seventeen years. By this criterion, only 3 of 54 epileptic patients, or 5.5 per cent, became deteriorated. The incidence of mental impairment in the adequately treated group was smaller than in a larger, less adequately treated group.

SUMMARY

One hundred noninstitutionalized epileptic patients comprised our series. After thorough diagnostic studies they were given a battery of six psychologic tests, including the Stanford-Binet test. The mean intelligence quotient was 93, 7 points lower than the generally accepted average for a normal community. In the cases of cryptogenic epilepsy the average intelligence quotient was 97, but in those of the symptomatic type it was only 88. Most mental traits were normal except memory, attention and language ability, which were somewhat deficient. Tests containing primarily motor elements gave lower scores than was anticipated from the mental ability in most cases. The reaction time in free association tests was slower than in normal persons.

Patients treated with phenobarbital showed a marked reduction in the number of spells. In all, 79 per cent of 48 patients given phenobarbital for a year were either free from attacks or definitely improved. The treated patients, although more severely afflicted at the outset, had only 20 per cent as many convulsions as did the controls during the trial year, and only 15 per cent as many petit mal attacks.

Psychologic tests performed before and after one year of treatment with phenobarbital showed no impairment in the mentality of 48 epileptic patients. The control group of 42 epileptic persons likewise did not deteriorate. Seven patients were tested before and after two years of phenobarbital therapy. On the whole, the slight changes after two years of treatment were in the direction of normality. In 13 cases the first year was used as a control and phenobarbital was given throughout the second year. There was some improvement in performance with the psychologic tests after the year of treatment. This study therefore indicates that phenobarbital in doses of 1½ grains (0.1 Gm.) two or three times a day can be given for two years without resultant deterioration of the intellect.

2007 Wilshire Boulevard.

18. Paskind, H. A.: The Absence of Deteriorating Effects of Bromides in Epilepsy, J. A. M. A. **103**:100 (July 14) 1934.

RELATION OF VENTRICULAR ASYMMETRY TO CONTRACTING INTRACRANIAL LESIONS

J. S. ROBERTSON, F.R.C.S.
GLASGOW, SCOTLAND
AND
A. E. CHILDE, M.D.
MONTREAL, CANADA

It is well known that an expanding lesion involving one cerebral hemisphere almost invariably displaces the septum pellucidum and third ventricle toward the opposite side. In recent years a voluminous literature has accumulated in connection with expanding intracranial lesions. Much less has been written concerning atrophic and contracting lesions. Dandy [1] mentioned that after destruction of the brain there is ventricular dilatation, sometimes local and sometimes general. He also stated that in such cases dilatation of the subarachnoid space is seen at operation. Foerster and Penfield [2] recognized that ventricular displacement occurred in patients with epilepsy and expressed the belief that this was due to "brain-pull or ventricle-pull" from scar tissue. They concluded that atrophy alone could not be responsible. Dyke, Davidoff and Masson [3] reported a group of cases of infantile hemiplegia in which there were thickening of the skull and overdevelopment of the sinuses on the side of the affected lobe of the cerebrum. In these cases they stated that the lateral ventricles and the third ventricle were displaced toward the affected side. They did not present any evidence as to whether the displacement was purely on an atrophic basis.

The present investigation has been undertaken to determine, if possible, whether displacement of the septum pellucidum and third ventricle

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From the Department of Neurology and Neurosurgery, McGill University, Montreal, and the Montreal Neurological Institute.

1. Dandy, W. E.: The Space-Compensating Function of the Cerebrospinal Fluid: Its Connection with Cerebral Lesions in Epilepsy, Bull. Johns Hopkins Hosp. **34**:245, 1923.

2. Foerster, O., and Penfield, W.: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

3. Dyke, C. G.; Davidoff, L. M., and Masson, C. B.: Cerebral Hemiatrophy with Homolateral Hypertrophy of the Skull and Sinuses, Surg., Gynec. & Obst. **57**:588, 1933.

toward an intracranial lesion indicates the presence of adhesions between the dura and the pia-arachnoid or whether such displacement may not be due to simple atrophy unaccompanied by the formation of a cicatrix.

MATERIAL

A group of patients were chosen who were first studied by encephalographic, or occasionally by ventriculographic, means and were later submitted to craniotomy. Nearly all suffered from epilepsy. It was necessary to reject a considerable percentage of these for one or more of the following reasons:

1. No true anteroposterior roentgenograms available. When there was sufficient rotation of the head to produce a shift of the septum pellucidum of more than 1 mm. it was found that this rotation could be readily recognized.

2. Incomplete visualization, due to inadequate filling of the ventricles.

3. Previous craniotomy. In such cases there was frequently a bone defect in the skull which altered its contour. It is thought that post-traumatic atrophy

TABLE 1.—*Distribution of Patients*

Group of Patients	Number
Normal	17
Lesion at 12 years or over	24
Lesion at 2 to 12 years of age	20
Lesion under 2 years of age	16
Patients with porencephaly	7
Total	84

may have resulted from handling the brain at the time of operation and that this would confuse the effect of the primary lesion.

4. Considerable subdural escape of gas revealed by pneumoencephalogram or subdural fluid seen at operation.

5. Possible neoplastic lesion.

6. Bilateral lesions.

7. Operative exposure too limited to permit reasonable assurance that all the lesion had been exposed.

As may be seen in table 1, 84 suitable cases were analyzed. In 7 instances, large cysts communicated with the ventricles or with the subarachnoid space, and these cases have been placed in a separate group. In 17 of the remaining 77 cases the condition was classified as normal. In the normal group either no pathologic condition was observed at the time of operation, or the lesion, if found, was very minute and in some cases its existence was questionable. This group was used to determine how much deviation of the septum pellucidum and third ventricle can be accepted as within normal limits.

The remaining 60 cases were divided into three groups: (*a*) those in which, according to the history, the lesion in question occurred at some time after the age of 12 years, when growth of the skull is reasonably complete; (*b*) those in which the lesion occurred at some time between the second and the twelfth year, when growth of the skull is occurring rather slowly, and (*c*) those in which the lesion occurred before the age of 2 years, when the skull is growing rapidly.

METHODS

To avoid prejudice, the encephalograms were measured without knowledge of the history and operative observations.

Measurements were made from the outer table of each side of the skull to the superior portion of the septum pellucidum, in a plane parallel to the base. When the septum pellucidum was more markedly deviated in its lower than in its upper portion (which was unusual) it was measured superiorly and inferiorly and an average taken. Similarly, the distance of the center of the superior portion of the third ventricle from the outer table of each side of the skull was measured. The differences between the corresponding measurements were then divided in half to obtain the actual shift of the ventricular midline. In the following tables the shift represents the displacement of the ventricular midline toward the lesion. In the few cases in which a shift occurred away from the lesion the displacement is indicated as a minus value.

TABLE 2.—*Data on Normal Group*

Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.
28	0.0	0.0
71	0.0	0.0
74	0.0	0.0
89	0.0	0.0
12	0.0	0.5
73	0.0	0.5
121	0.0	0.5
115	0.5	0.0
116	0.5	0.0
60	0.5	0.5
139	0.5	0.5
40	1.0	0.0
99	1.0	0.0
32	1.0	0.5
82	1.0	1.0
102	1.0	1.0
112	1.0	1.0
Averages	0.5	0.3

RESULTS

Cases of Normal Type.—The number of strictly normal cases is few, as craniotomy, in the absence of suggestive roentgenographic findings, was carried out only when there was unequivocal clinical evidence. This group includes instances in which exploration yielded normal (or practically normal) results. As shown in table 2, there were 17 such cases, and in these the measured shift of the septum pellucidum and third ventricle did not exceed 1 mm. The average shift of the septum pellucidum amounted to 0.5 mm. from the midline, and that of the third ventricle to 0.3 mm. Consequently it has been assumed that measurements in cases of abnormal type in which there was a shift of 1 mm. or less should not be taken as significant.

Cases of Abnormal Type.—It was decided to segregate cases in which no definite shift was presented from those in which the condition was abnormal, so that the positive findings would not be unduly diluted. The cases in which there was a shift were then divided on the basis of the presence or absence of adhesions observed at operation. In the cases of adhesions there were either dense bands of scar tissue passing into the brain substance from the dura or close adhesion between the dura and the pia-arachnoid. Cases in which there were long, tenuous adhesions and/or vessels passing between the pia-arachnoid and the dura, without other adhesions, were included in the group of simple atrophy as in these there was no evidence of effective anchorage between

TABLE 3.—*Data in Cases in Which Lesions Occurred at Age of 12 Years or Over*

Atrophy with No Adhesions			Atrophy with Adhesions			Adhesions and Slight Atrophy		
Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.	Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.	Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.
67	4.5	3.0	107	6.0	6.5	14	1.0	X*
11	3.0	3.0	65	5.5	2.0	31	0.0	X
16	3.0	2.5	49	2.5	3.0	43	0.0	0.0
95	1.5	1.5	38	2.0	4.0	81	0.5	0.0
20	1.5	1.5	132	2.5	4.5	104	0.0	0.0
90	1.0	0.0	93	2.5	X	18	0.5	0.0
36	Asymmetric skull		72	3.0	—0.5			
45	Asymmetric skull		52	2.0	1.0			
Average of			85	1.5	X			
5 abnormal			75	1.5	0.0			
cases	2.7	2.3	Average	2.9	2.9			

* In this table and in tables 4, 5 and 6 X indicates absence of data.

the brain and the dura. However, the inclusion of these cases either with those of atrophy or with those of adhesions, or their complete exclusion, does not alter the findings significantly, as in none of them, as it happened, was there any marked shift. In almost all the cases in which there was merely cerebral atrophy a definite shift was presented. This is partially due to the fact that the cases of minor degrees of atrophy were included in the normal group. On the other hand, there were several cases of definite adhesions in which no real shift was demonstrated.

Group A: As shown in table 3, this group has been divided into cases of atrophy with no adhesions and cases of atrophy plus adhesions (fig. 1). It will be seen that the degree of shift of the septum pellucidum and third ventricle was comparable in these two divisions. There was no significant difference in the amount of shift in the cases in which there were cicatrices and in those in which there were none. A third

division of 6 cases, in which there were adhesions and slight atrophy, is even more interesting. In none of these cases was there a definite shift of the ventricular midline, although real adhesions were seen at operation. This tends to show that the presence of adhesions per se will not necessarily produce displacement of the ventricular midline. In each case in this division, dense adhesions passed from the dura into the brain for a variable distance, sometimes reaching almost as far as the wall of the lateral ventricle.

Group B: As shown in table 4, these cases have been divided in the same manner as those in the preceding group. They include cases

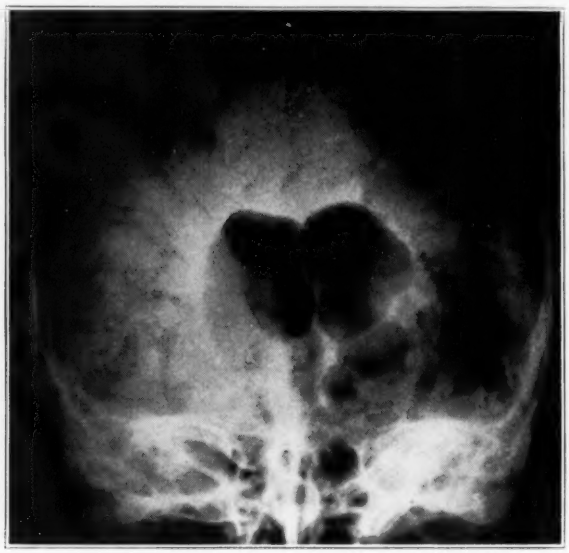

Fig. 1.—O. M., aged 29 years. The septum pellucidum is shifted 5.5 mm. from right to left, and the third ventricle is shifted 2 mm. in the same direction. The patient was struck by a train eight years ago, and for the past five years there had been epileptic seizures. A meningocerebral cicatrix involving the left frontal lobe, as well as marked cerebral atrophy, was observed at operation.

in which, according to the history, the lesion occurred between the second and the twelfth year. The findings in this group corresponded closely to those in the adult group. In case 26, in which there was atrophy, an extremely marked shift of the septum pellucidum was presented. When allowances are made for this, it will again be seen that the shift of the septum pellucidum was approximately the same in cases of atrophy and no adhesions as in cases of atrophy plus adhesions. The shift of the third ventricle in the group of cases of adhesions is rather unreliable, as measurements were available in only 4 of 6 cases. A

third division was again made, including 4 cases in which there were definite adhesions but no shift.

Group C: This includes cases in which the history indicated that the lesion occurred at some time between birth and the age of 2 years; the results are shown in table 5. Almost all the skulls were found to

TABLE 4.—*Data in Cases in Which Lesions Occurred Between Ages of 2 to 12 Years*

Atrophy with No Adhesions			Atrophy with Adhesions			Adhesions and Slight Atrophy		
Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.	Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.	Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.
26	9.0	X	114	2.5	X	50	1.0	0.5
119	2.5	5.0	68	0.0	3.0	7	0.5	0.0
15	2.0	3.0	17	2.0	X	108	0.0	0.5
78	2.0	0.5	64	2.0	0.0	55	0.5	—1.0
33	1.0	2.0	98	2.0	—0.5			
37	0.5	1.5	63	1.5	0.5			
137	0.5	1.5						
103	1.0	1.0						
139	0.5	0.5	27	Asymmetric skull				
Average of abnormal cases	2.5	2.3	Average of 6 cases	1.7	0.7			

TABLE 5.—*Data in Cases in Which Lesions Occurred Before 2 Years of Age*

Atrophy with No Adhesions			Atrophy with Adhesions		
Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.	Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.
3	8.0	X	109	20.0	8.0
106	7.0	9.0	30	7.5	7.5
101	7.0	9.0	29	2.0	6.5
117	6.0	4.5	138	3.0	1.0
88	6.0	3.0	96	1.5	1.5
86	6.0	X			
118	5.5	3.5			
83	5.0	3.5			
13	2.5	6.0			
113	2.5	2.0			
80	2.0	3.0			
Average	5.2	4.8	Average	6.8	4.9

be asymmetric, and consequently the measurements are not strictly comparable with those in the two previous groups (fig. 2). For purposes of comparison, however, a table of measurements has been made to give an idea of the magnitude of the lesions that occurred. When the lesion was of any considerable extent the ipsilateral side of the skull was decreased in volume and usually flattened. Often the falx was visualized and, by measurement, displaced toward the side of the lesion.

When the position of the falx was checked in relation to the sutures and the base of the skull, it was found that its superior attachment was still in the anatomic midline. When an anatomic midline was drawn from the crista galli to the superior attachment of the falx, the central portion of the falx sometimes lay in this line, and sometimes it was slightly bowed toward the side of the lesion. Nearly always the area of the affected side of the skull, as shown in anteroposterior roentgenograms, was decreased on the side of the lesion. Often the septum pellucidum and the third ventricle lay in the line of the falx, but in a few cases they deviated toward the lesion, even beyond this line. This occurred not only in cases in which there were adhesions but also in cases in which there was atrophy without adhesions; unfortunately,

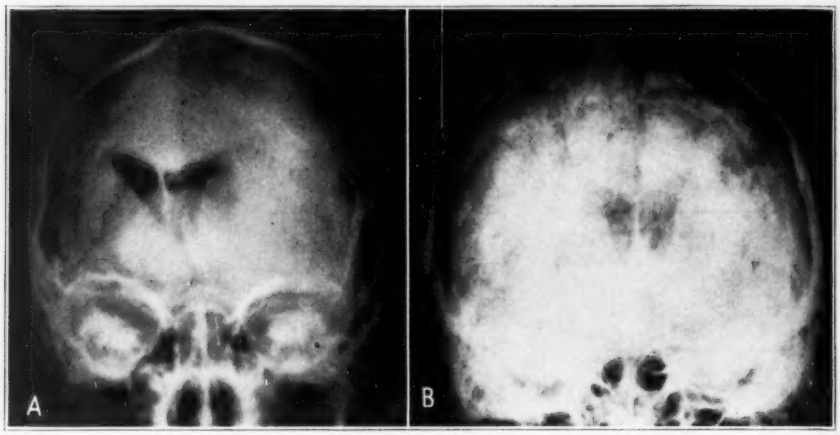

Fig. 2.—*A*, D. D., aged 14 years. The septum pellucidum is shifted 20 mm. to the right of the midline, and the third ventricle is shifted 8 mm. to the right. The right side of the cranium is flattened and much smaller than the left. The left arm and leg had been weak ever since convulsive seizures four days after birth, and seizures had occurred on the left side for the past three years. Operation revealed marked cerebral atrophy as well as a meningocerebral cicatrix, involving particularly the right postcentral gyrus. *B*, C. A., aged 24 years. The septum pellucidum is 6 mm. to the left of the midline, but the displacement is not so marked when its position is reckoned in relation to the anatomic midline. The left side of the cranium is smaller than the right, and the falx is bowed to the left. Convulsions occurred for one week after a birth injury, and development of the right arm and leg was impaired. There had been convulsive seizures, beginning in the right hand, for the past eleven years. Several cerebral cysts, as well as cerebral atrophy, were seen in the left parietal lobe at operation.

however, the number of such cases is too limited to warrant any final conclusions. Corresponding to the previous two groups, the shift of the septum pellucidum and third ventricle was approximately the same

in the group in which there were atrophy and adhesions as it was in the group in which there was atrophy without adhesions.

Porencephaly.—When a large cyst communicated with the subarachnoid space or with the ventricles there was a much smaller shift than one would expect from the size of the lesion (fig. 3). This was illustrated in 7 cases, which have been included in one group (table 6). In 4 of these cases the shift was negligible or absent, while only in 2 was there any real displacement. In these cases the loss of cerebral substance was in part compensated for by the accumulation of fluid in the cyst.

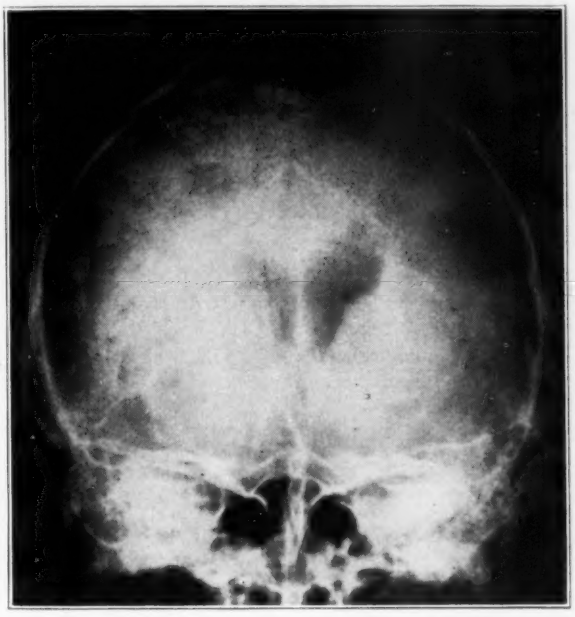

Fig. 3.—J. B., aged 13 years. A porencephalic area is shown in the left hemisphere. The septum pellucidum is shifted 3.5 mm. from right to left, and there is enlargement of the left lateral ventricle. Weakness of the right side of the body, associated with convulsions, occurred at the age of 3 months. Cerebral atrophy and meningocerebral cicatrix involving the left postcentral convolution were observed at operation.

Cerebral Vascular Occlusion.—Additional evidence, particularly regarding cerebral atrophy, was obtained from cases in which clinical evidence of cerebral vascular occlusion was presented. In 4 such cases encephalographic examination was performed at least two years after the occurrence of symptoms. In only 1 of these cases has there been a craniotomy, but in the other 3, as judged from purely clinical evidence,

there is no reason to believe that any adhesions have formed. In 2 of these cases, as shown in table 7, there was evidence of marked atrophy. In the third case there was only slight shift, while in the fourth there was no shift at all. In the last case an encephalogram revealed a large subarachnoid collection of fluid, which apparently prevented a shift from occurring, in a similar manner to that noted in the group of cases of porencephaly.

Anomalous Cases.—It was noted that in some of these cases, both those of adults and those of children, there was an apparent shift of the third ventricle, and occasionally of the septum pellucidum, away from

TABLE 6.—*Data on Cases of Porencephaly*

Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.
66	3.5	2.0
76	3.5	X
105	—0.5	2.5
91	0.5	0.0
54	0.0	0.0
111	0.0	0.0
41	0.0	0.0

TABLE 7.—*Data on Adults with Cerebral Thrombosis*

Case No.	Shift of Septum Pellucidum, Mm.	Shift of Third Ventricle, Mm.
130	6.0	6.5
129	5.0	6.5
128	1.5	1.5
140	0.0	0.0
Average of abnormal cases	4.2	4.8

the side of the lesion. In all such cases asymmetric heads were found, and they present a somewhat different problem. In these patients projection of the anatomic cranial midline from the crista galli to the falx, if seen, or from the sagittal suture, if the falx was not visible, revealed that the septum pellucidum and third ventricle either were in the cranial midline or were displaced toward the lesion. Owing to the asymmetry of the skull, measurements were unreliable. These cases are unlike those described in group C (of children from birth to 2 years of age) in that the volumes of the two sides of the skull were approximately equal, while in group C one side was smaller than the other. From these observations it seems that in some cases at least actual measurement of the cranial midline from the sides of the skull is unreliable and that projection of the true anatomic midline is more accurate.

CONCLUSIONS

1. When an atrophic lesion occurs in one cerebral hemisphere after the period of rapid growth of the skull there may result a shift of the septum pellucidum and third ventricle toward the side of the lesion. Such a shift does not necessarily indicate the presence of adhesions. It is modified by compensating collections of fluid, as in cases of porencephaly, subarachnoid and intracerebral cysts and enlargement of the lateral ventricle on the side of the lesion. Adhesions may accentuate a shift by the prevention of subarachnoid collections of fluid or porencephaly.

2. The amount of shift of the ventricular midline appears to be dependent on the uncompensated loss of cerebral substance. It is doubtless also dependent, to some extent, on the site of the lesion. As the exact extent of the lesion cannot be accurately estimated, comparative estimates for different sites are impossible.

3. During the period of rapid growth of the skull the presence of a lesion resulting in the loss of cerebral substance causes a relative reduction in the rate of growth of the ipsilateral side of the skull.

4. In an asymmetric skull which is not the result of an early cerebral lesion it is more reliable to estimate the shift of the septum pellucidum and third ventricle from the true anatomic cranial midline than to rely on measurements to the outer table of the skull.

RELATION OF ANOXEMIA TO EARLY ACTIVITY IN THE FETAL NERVOUS SYSTEM

W. F. WINDLE, PH.D.
AND
R. F. BECKER, M.S.
CHICAGO

There are essentially two conceptions of early development of somatic movements in mammalian embryos. One group of investigators, Coghill, Angulo y Gonzáles, Hooker and their colleagues,[1] have expressed the belief that they have demonstrated the genesis of reflex activities by a process of "individuation" from an already integrated total reaction, or pattern; in other words, that more or less discrete movements are not the primary units but that these break off, as it were, from some sort of a mass movement that constitutes the basic pattern of behavior. Another group of investigators, Carmichael, Windle and their associates,[2] have expressed the opposing view that relatively simple activities manifest themselves first and that these become integrated during further growth in the nervous system, so that the more complex reactions of older fetuses are built up from the less complicated ones of the younger. The issue is clearly drawn, and it is of fundamental importance to an appreciation of the later stages in development to submit these theories to such tests as will bring forth the facts in each case.

During the past two years, we have had occasion to reexamine the question of early development of somatic behavior, paying particular attention to the oxygen supply of the fetus and mother and to the effects

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From the Anatomical Laboratory of the Northwestern University Medical School.

1. (*a*) Coghill, G. E.: Anatomy and the Problem of Behavior, New York, The Macmillan Company, 1929, pp. 11 and 113. (*b*) Angulo y Gonzáles, A. W.: The Prenatal Development of Behavior in the Albino Rat, J. Comp. Neurol. **55:** 395, 1932. (*c*) Hooker, D.: Early Fetal Activity in Mammals, Yale J. Biol. & Med. **8:**579, 1936.

2. (*a*) Carmichael, L.: Origin and Prenatal Growth of Behavior, in Murchison, C. A.: A Handbook of Child Psychology, Worcester, Mass., Clark University Press, 1933, chap. 2, pp. 31-159. (*b*) Windle, W. F.; Orr, D. W., and Minear, W. L.: The Origin and Development of Reflexes in the Cat During the Third Fetal Week, Physiol. Zool. **7:**600, 1934.

of anesthesia and the technical procedures used in studying fetuses. We shall present the results of these experiments together with our interpretation of them. We hope that we can put the story of the relationship of simple reflexes to mass movements into words as clearly as it was manifested to us at the time of experimentation.

MATERIAL AND METHODS

Major consideration will be given to the results of experiments in 95 embryos and fetuses of 21 decerebrate cats during the ten day period following the first appearance of somatic activity, i. e., at an insemination age of from 23 to 33 days. In 12 of the animals mating was observed in the laboratory. The embryos and fetuses varied in crown-rump length from 12.5 to 38 mm. when measured in the fresh condition at the conclusion of experiments. They varied from approximately 0.1 to 3 Gm. in fresh weight. The greatest number of experiments were performed on fetuses between 25 and 30 days old. This is the period in prenatal life during which growth of integrating factors in the central nervous system is especially active.

Minor consideration will be given to experiments on 25 or 30 other specimens of similar ages which were studied under conditions of general anesthesia. Observations on several hundred fetuses larger than those of our principal series have influenced our studies, but these will not be dealt with specifically at this time.

The method of decerebrating the pregnant cats for study of their fetuses was the same in all instances. The animals were first anesthesized with ether. The carotid arteries were ligated high in the neck, it being ascertained that the blood flow to the brain from these sources was stopped. A tracheal cannula was inserted to facilitate the next step in the operation. An incision was then made through the soft palate and mucous membrane on the roof of the nasopharynx and a small hole drilled through the cranium between the two tympanic bullae. After the dura mater was incised and the cerebrospinal fluid allowed to escape, a ligature was passed under the basilar artery at about the middle of the pons, and the vessel was tied. The method has been described in detail elsewhere.[3]

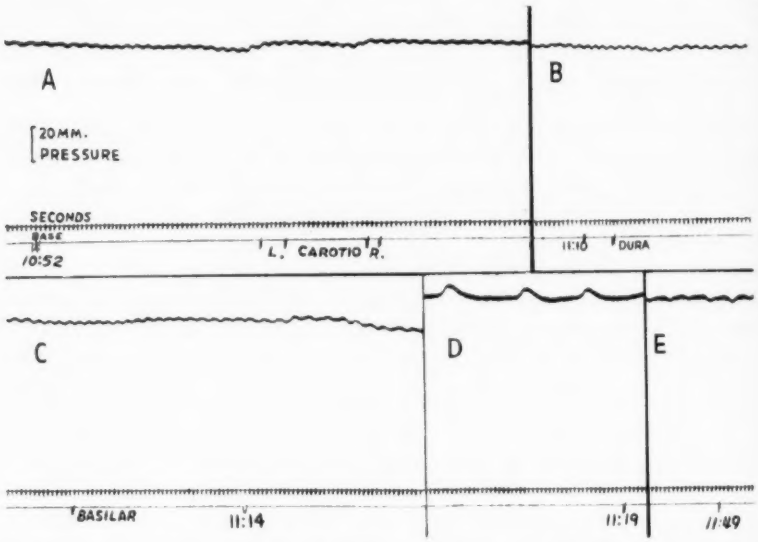
This method of decerebration rendered the animals unconscious without seriously disturbing other physiologic functions. No evidence of surgical shock was observed, for when continuous records of the animals' blood pressure were made before, during and for long periods after the operation it appeared that this was maintained at a high level. Portions of such a record are reproduced in the accompanying figure. Respiration, shown as larger, secondary waves in the tracings (the rapid pulse waves are ill defined in the reproduction as reduced), usually slowed considerably after the basilar artery had been tied and the anesthetic discontinued, but in the majority of cats its rate increased within an hour. In the animals there developed rigidity characteristic of the decerebrate state when the anesthetic was discontinued after the operation. In some this was only transient, however, because occasionally sufficient blood made its way by collateral vessels anastomosing over the surface of the pons and cerebellum to result in a meager flow to the midbrain, part of the diencephalon and perhaps a little of the cerebral cortex. But we never encountered results indicative of a return of consciousness

3. Pollock, L. J., and Davis, L. E.: Studies in Decerebration: An Acute Decerebrate Preparation, Arch. Neurol. & Psychiat. **12**:288 (Sept.) 1924.

after all ligatures had been properly applied. In consequence of this fact, it was possible to proceed with experimentation in the fetuses without further use of anesthesia. One or two hours (occasionally longer) was allowed for recovery from the ether used during decerebration.

The advantages which this method has over others should be evident. There is no period of shock such as follows section of the spinal cord. The surgical manipulations involved can be carried out in twenty to twenty-five minutes with loss of less than 1 cc. of blood, and that from the mucous membranes rather than within the cranium. No further anesthetic is necessary, and drugs of other types need not be employed. The animals are usually quiet and unresponsive to manipulations of the viscera at the time of experimentation.

Observations of fetal activity were conducted with the decerebrate cats fastened securely in a constant temperature bath filled with Locke's solution at body tempera-



Portions of one record of blood pressure in a female cat taken before, during and after ligation of the carotid and basilar arteries, in decerebrating the animal by the Pollock-Davis method. Ether anesthesia was discontinued after tying the basilar artery, and gradual slowing of respiration can be observed; the respiratory rate increased and was 13 per minute at 11:50 a. m. The occlusion of the carotid arteries by double ligatures is shown by signal marks in *A*; the incision of the dura mater, exposed through the roof of the pharynx, in *B*, and the ligature of the basilar artery, in *C*.

ture. It has been demonstrated [4] that ordinary physiologic saline solutions lacking calcium and potassium are entirely unsatisfactory for studying early fetal movements because ionic unbalance resulting from diffusion of these elements from the delicate fetal tissues introduces certain spontaneous activities which seem not to involve the central nervous system at all.

4. Windle, W. F.: Calcium and Potassium Deficiency as Possible Causes of Certain Delayed Fetal Movements, Physiol. Zool. **12**:39, 1939.

OBSERVATIONS

The youngest cat embryos, 12.5 to 15 mm. in crown-rump length, presented few somatic movements even under the best of conditions. At the moment of incising the uterus (i. e., in the first five to thirty seconds), and before the amnion was opened, we were frequently able to elicit one or two responses. When the swollen amniotic sac containing an embryo was percussed with a probe the forelimb on the side toward the observers moved. This movement resembled a jerk and was always a backward and outward extension. Another response less commonly elicited was a quick movement of the head to the side and backward. This seldom followed tapping on the amniotic sac, but could often be elicited by direct stimulation at the tip of the snout. The movement of the forelimb was elicited both by tapping on the amnion and by stroking or touching the limb with a dental broach, or even with a single horsehair stimulator passed through the amnion. The two movements were unintegrated at the time they first could be obtained. In 15 mm. specimens the movement of the head sometimes followed that of the limb, but the converse was never the case. We have designated them as simple responses.

These simple movements have been described before,[2b] and detailed consideration has been given to their nature and to correlation between their appearance and the genesis of reflex arcs in the central nervous system.[5] In the present studies we have endeavored to learn how they are related to the oxygen supply of the fetus. The fact that they were elicitable by light forms of stimulation for only a minute or two at best after the specimens had been brought into view, even when every precaution was taken to preserve the attachment of the placentas, and that when our efforts were clumsy and slow they often failed to be manifested suggested that the disturbance in the normal physiologic relationship of embryo to uterus had much to do with their disappearance. Therefore we deliberately set up states of anoxemia in the mother's, and consequently in the fetuses' blood as well, by administering a mixture of approximately 5 or 7 per cent oxygen in nitrogen from a gas anesthesia machine to the cats by tracheal cannula. The uteri soon became appreciably cyanotic and were then quickly incised. In no instance were we able to elicit limb responses of the embryos under these conditions, but occasionally strong stimulation of the snout produced an extension of the head. It seemed that the anoxemia had effectively depressed the irritability of the embryos. In 1 experiment we administered a mixture of about 5 per cent carbon dioxide in 95 per cent oxygen to the decerebrate cat. Its respiration increased in depth, and the vessels on the uterus seemed a little redder than before. When the uterus was opened, the fetuses gave responses which were appreciably better than were usually encountered while the cats were breathing air; the specimens were more irritable, but the activities of head and forelimbs were still unintegrated. With decreasing irritability, as the time after delivery lengthened, stronger stimuli were required to produce results.

In the period during which the embryo grows in length from about 16 to 25 mm. a number of other simple responses are added to its behavioral repertoire. Invariably, these could be elicited as separate twitches (e. g., of the hindlimb, tail or wrist) before they became integrated with earlier responses. As in the earlier stages, it was only during the first part of the observation period that their manifestation could be easily induced.

5. Windle, W. F.: Correlation Between the Development of Local Reflexes and Reflex Arcs in the Spinal Cord of Cat Embryos, J. Comp. Neurol. **59**:487, 1934.

Not uncommonly, "spontaneous" movements were seen during the early moments after the specimens were exposed. It seemed probable that they were actually elicited by the manipulations of the fluid-filled vesicles. Such activity usually consisted of side to side movements of the head and neck, involving to some extent the shoulder muscles and, in larger specimens, part of the trunk and even the hindlimbs. These movements were arrhythmic in the smaller specimens, and never did they resemble the respiratory-like activities of small sheep fetuses.[6] The degree of participation of appendicular muscles in the spontaneous movements varied considerably, but was never great. There was no doubt that contractions of the neck and trunk muscles predominated.

We have long been impressed by the apparent variation encountered in the degree of integration of movements in specimens under different physiologic conditions. Deliberateness in dissection of the uterus often resulted in the bringing forth of an embryo in which stimulation failed to elicit separate, individual movements. But when the operation was performed very quickly we could obtain separate twitches of many groups of muscles, even though these groups came into play in the integrated activities as the fetal irritability declined. It was evident that factors other than type, or even strength, of stimulus used were influencing the nature of the responses in the specimens under consideration. Consequently, an attempt was made to alter the atmosphere breathed by the mother to see what effect the resulting changes in the fetal blood might have on fetal behavior.

Consistent results followed deprivation of adequate oxygenation, accomplished by having the cats breathe a mixture of about 5 to 7 per cent oxygen in nitrogen. Fetuses which had been delivered before oxygen want was manifested by the cats gave the usual separate, individual responses to percussing, touching or stroking. But at the very moment of appearance of the maternal respiratory response to the gas mixture, the fetuses became less irritable to light forms of stimulation, and stronger stimuli gave integrated movements only. In 1 experiment we were able to bring about recovery of irritability in the fetus by quickly substituting forced ventilation with pure oxygen for the mixture of nitrogen and oxygen, the individual movements returning when this had been done.

When a state of oxygen deficiency was set up before opening the uterus, the fetuses invariably showed spontaneous movements of a tonic, sustained character at the moment they were exposed. Their irritability was slight. Stimuli which were adequate at all resulted in strong, sustained contractions of the neck and trunk muscles, and the limbs moved at the shoulder with the trunk. In short, under duress of oxygen deprivation the fetuses exhibited "mass reaction" exactly like that so admirably illustrated in motion pictures of fetuses by several investigators. Extended use of the gas mixture or further lowering of its oxygen content soon brought about more complete fetal asphyxia, in which all responses ultimately ceased. However, the mass reactions first tended to break down, as it were, and progressively fewer muscle groups participated in them as asphyxia was prolonged.

In the larger members of the series (23 to 25 mm. long) anoxemia seemed to heighten irritability at first, but this was transient. The specimens soon failed to respond to light forms of stimulation and exhibited spontaneous mass movements of the sustained type.

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6. Barcroft, J., and Barron, D. H.: The Genesis of Respiratory Movements in the Foetus of the Sheep, J. Physiol. **88**:56, 1936.

Carbon dioxide mixed with 93 to 95 per cent oxygen was given to several cats to breathe. The usual procedure was to observe one or two fetuses of a litter while the animal breathed air and then to study the remainder under this gas mixture. At the start, when the mother's respiration was first stimulated by the carbon dioxide, the fetal activities were usually easier to elicit by touching or by light percussion than they had been previously. In some cases the lightest touch of the limbs, with a single horsehair passed through the amnion, brought about local twitches of the limbs. Reflex movements of the opposite limbs sometimes occurred in response to similarly applied stimuli. Strong stimulation resulted in quick movements of several parts, such as the head, both forelimbs at the shoulder and the trunk. These occurred simultaneously or in rapid sequence, suggestive of a spreading wave of conduction from points stimulated. In the larger members of the series the response to strong stimuli resembled the squirming of newborn kittens aroused from sleep. In all specimens, at the beginning of observation and when the carbon dioxide concentration was less than about 7 per cent, it was possible to obtain local activities by employing light forms of stimulation without setting up the integrated mass movements. When the amount of carbon dioxide in the atmosphere breathed by the mother cats had been increased above 10 per cent, irritability of the fetuses was definitely decreased and almost all responses to stimulation were mass movements, usually of the sustained or tonic type.

Spontaneous activity was encountered more frequently when the uterus was opened while the cat was breathing an atmosphere containing 5 to 7 per cent carbon dioxide than while it was breathing air. The movements were less tonic than with higher concentrations (10 to 15 per cent) of the gas.

Rhythmic activities were encountered for the first time [7] in cat fetuses measuring 28 mm. in crown-rump length and weighing about 1.5 Gm. These were movements of the abdominal, thoracic and diaphragmatic muscles, occurring at rates as rapid as 2 per second and resembling respiration. Unlike the sheep fetuses,[6] in which respiratory-like movements at first involved extension of the head and trunk, the appearance of this behavior reaction in the cat was not related to the activity of the neck muscles. It sometimes occurred spontaneously several minutes after the specimens had been delivered, but while the placentas were still attached to the uterus. It was elicited promptly by administering to the mothers atmospheres low in oxygen or containing 5 to 7 per cent carbon dioxide.[8] When the concentration of carbon dioxide was increased or when prolonged or severe oxygen deficiency was produced, the rapid rhythmic movements in question stopped or became slow rhythmic gasps. The gasps involved extension of the head and trunk with contractions of the respiratory muscles, and as the severity of the anoxemia increased extension of the head changed to flexion with each gasp.

INTERPRETATION

It seems that cat embryos and fetuses at an insemination age of 23 to 33 days [9] are capable of responding to various forms of stimulation. We do not know whether or not they actually perform movements in

7. Some of the side to side movements of the head and trunk occurred in imperfect rhythms in specimens about 25 mm. long.

8. Windle, W. F.; Monnier, M., and Steele, A. G.: Fetal Respiratory Movements in the Cat, Physiol. Zool. **11**:425, 1938.

9. The gestation period in the cat is from sixty-five to sixty-nine days.

utero under perfectly normal physiologic conditions at this stage in fetal life. But when specimens are examined under conditions which are as close to physiologic as we can make them, we find that they are relatively quiet and that it is possible to elicit a number of separate and distinct responses. These at first are not integrated, bear little relation to one another, possess some individuality in regard to the type of adequate stimulus and simulate local reflexes. That they are, indeed, reflexes seems clear.[10] Throughout the period of development under consideration, the individuality of many of the responses is never entirely lost, although integration, especially in the axial group of muscles, begins to manifest itself early.

The irritability of the early fetal nervous system varies with conditions of respiratory metabolism. It is enhanced to some extent in the early stages of increasing the carbon dioxide level or decreasing the oxygen level of the fetal blood. Toward the end of the part of the fetal period under consideration, rhythmicity of response enters into the picture as a function of partial anoxemia. More severe degrees of asphyxia or further elevation of the carbon dioxide level leads to depression of irritability on the afferent side of the fetal nervous system and to the simultaneous discharge of larger and larger groups of motor neurons, either "spontaneously," presumably through some form of direct chemical stimulation, or in response to strong stimulation of afferent neurons. Thus, one encounters a mass reaction or pattern in the same specimens which showed localized responses when physiologic conditions were better. This mass reaction varies in appearance to some extent. It may be a rather quick total contraction with prompt relaxation or, as the anoxemia increases, a sustained total contraction. Sometimes it is so tonic that the fetus resembles a decerebrate animal. With extreme degrees of asphyxia complete depression of fetal activity is reached; but the last movements to go appear to be those which are most useful after birth, the movements used in forced inspiration (gasping). Long after all neural activity has ceased the heart continues to beat, but even after it has stopped skeletal muscles can be made to contract when stimulated directly by faradic shocks.

COMMENT

How do other studies on early fetal behavior fit into the concept we have presented? The theory of development from a mass reaction, or total pattern, was first applied to mammalian fetuses by Coghill,[11]

10. Windle, W. F.: On the Nature of the First Forelimb Movements of Mammalian Embryos, Proc. Soc. Exper. Biol. & Med. **36**:640, 1937; footnote 5.

11. Coghill, G. E.: The Early Development of Behavior in Amblystoma and in Man, Arch. Neurol. & Psychiat. **21**:989 (May) 1929.

when he attempted to correlate his own observations on embryos and larvae of the salamander Amblystoma with those of other investigators on the human fetus. These studies of Minkowski [12] and others on the human fetus were all made on specimens removed from the uterus, and the results were certainly influenced by marked asphyxia. They correspond to our observations on cat fetuses delivered from the cyanotic uterus which demonstrated clearly the total, sustained behavior characterizing the mass reaction. If such were the only type of behavior that could be observed under all physiologic conditions, we, too, should favor the Coghill theory.

The first observations on cat fetuses reported from this laboratory [13] lent support to the theory of development from a total pattern. At that time (nine years ago) one of us (W. F. W.) and his associates were concerned primarily with studying the activities which fetuses engaged in "spontaneously" when delivered with intact placental circulation. The technic used to prepare the animals for experimentation was not as favorable as that we have used subsequently. But, as we have pointed out already, much of the "spontaneous" fetal behavior manifests itself under duress of partial anoxemia, when not all the functions of which specimens are capable are demonstrable.

It was only after we had perfected a technic for studying fetuses under better physiologic conditions and bent our efforts toward examining them during the first seconds to few minutes after exposure that we were led to an appreciation of the simple reflex movements which we have described in cat, rat and sheep embryos.[14]

Coghill's theory of behavioral development was supported by experiments on rats by Angulo y Gonzáles. The fetuses were delivered with placental circulation still intact, but this does not mean that they were receiving blood from the placentas as well oxygenated as it may have been before the uterus was opened. This point has been adequately proved in Barcroft's laboratory, where it was shown that fetal blood drawn without removing lambs from the uterus tends to have a high saturation with oxygen, often as much as 90 per cent or more.[15] How-

12. Minkowski, M.: Ueber frühzeitige Bewegungen, Reflexe und muskuläre Reaktionen beim menschlichen Foetus und ihre Beziehungen zur foetalen Nerven- und Muskelsystem, Schweiz. med. Wchnschr. **52**:721 and 751, 1922.

13. Windle, W. F., and Griffin, A. M.: Observations on Embryonic and Fetal Movements of the Cat, J. Comp. Neurol. **52**:149, 1931.

14. (*a*) Windle, W. F.; Minear, W. L.; Austin, M. F., and Orr, D. W.: The Origin and Early Development of Somatic Behavior in the Albino Rat, Physiol. Zool. **8**:156, 1935. (*b*) Barcroft, J.; Barron, D. H., and Windle, W. F.: Some Observations on the Genesis of Somatic Movements in Sheep Embryos, J. Physiol. **87**:73, 1936. (*c*) Windle, Orr and Minear.[2b]

15. Barcroft, J., and Mason, M. F.: The Atmosphere in Which the Foetus Lives, J. Physiol. **93**:22P. 1938.

ever, the blood of lambs delivered into a saline bath with the placental circulation still intact was often low in oxygen.[16] Steele and one of us (W. F. W.) also have found that saturation with oxygen of less than 50 per cent characterized the blood in the umbilical vein of exposed cat fetuses which were executing rhythmic, respiratory-like movements at the time.[17] Even if the rat fetuses in question were receiving adequately oxygenated blood, they had been removed and studied under general anesthesia. Etherized fetuses behave in respect to individual movements much as do etherized adult animals. Their irritability is depressed. Comparison of Angulo's motion picture demonstrations of activities of rat fetuses with the observations we have made during the early moments after delivering similar specimens leaves no doubt that conditions were very different in the two series of experiments.

The investigators who have avoided general anesthesia and who have made an effort to test fetal responses in the period immediately following delivery [18] have had no difficulty in observing individual responses in guinea pig and sheep embryos which were comparable with the individual responses in the cat and rat.[19] As a matter of fact, some of the unpublished observations in experiments with rat embryos performed by Swenson [20] ten years earlier, not readily accessible for study, seem to fit less well into the conception of development from a total pattern than into one of growing integration of lesser units.

The studies on human fetuses will bear consideration. The most complete recent series of experiments is that of the Pittsburgh laboratory.[1c] Specimens removed from the uterus at hysterotomy and subsequently observed as quickly as possible form the basis for conclusions favorable to the theory of behavioral development from a total pattern. In most cases general anesthesia was avoided. The fact that the specimens were no longer receiving oxygenated blood placed these observations in the same class with those in our own group of experiments performed with the fetuses in asphyxial states. We agree that sustained mass reactions characterize such fetuses. Recently, Fitzgerald, Webster and one of us (W. F. W.) [21] have had occasion to observe 3 human

16. (*a*) Barcroft, J.: Fetal Circulation and Respiration, Physiol. Rev. **16**: 103, 1936. (*b*) Barcroft, J.; Kramer, K., and Millikan, G. A.: The Oxygen in the Carotid Blood at Birth, J. Physiol. **94**:571, 1939.

17. Steele, A. G., and Windle, W. F.: Some Correlations Between Respiratory Movements and Blood Gases in Cat Foetuses, J. Physiol. **94**:531, 1939.

18. Bridgman, C. S., and Carmichael, L.: An Experimental Study of the Onset of Behavior in the Fetal Guinea-Pig, J. Genetic Psychol. **47**:247, 1935. Barcroft, Barron and Windle.[14b]

19. Windle, Orr and Minear.[2b] Windle, Minear, Austin and Orr.[14a]

20. Swenson, E. A.: The Development of Movement of the Albino Rat Before Birth, Thesis, University of Kansas, 1926.

21. Fitzgerald, J. E.; Webster, A., and Windle, W. F.: Unpublished data.

fetuses, 35 to 40 mm. in crown-rump length, under favorable conditions. The patients were given ¼ grain (0.015 Gm.) of morphine sulfate about an hour before operation. Hysterotomy was performed with local anesthesia induced with procaine hydrochloride. Observations were made on the fetuses as the uterus was being incised. They were then delivered, and other observations were made immediately. The activities characterizing the 3 specimens in utero were jerky, choreiform twitches of the hands, feet and head; they were very lively movements, and they seemed to possess a high degree of individuality. However, as soon as the placental circulation was interrupted the specimens began to show more sustained and tonic movements, with considerable squirming. Reflexes, such as flexor withdrawal of the hand and foot, extension of the contralateral arm, avoidance of facial stimulation, contraction of the orbicularis oculi muscle and abdominal contraction, were elicitable for some time, but all movements were less lively and more tonic and required stronger stimuli than they had in utero. We conclude, therefore, that the human fetus responds to conditions of anoxemia like those of other species which have been studied, and we believe that behavior will be found to have its genesis in man in the same progressive ontogenetic integration of relatively simple, unit reflexes as in the cat and other experimental mammals.

Recently, Kuo [22] attempted to study the effects of anoxemia on behavior in chick embryos. He has criticized the work of others in the field of behavioral development, stating that "among many defects of their data there has been a lack of control experiments." This investigator then proceeded to record experiments of his own, taking for his normal standards observations of movements and reactions which he could see in eggs that had been opened and had the shell membrane rendered translucent by coating it with petrolatum. Apparently, Kuo was unaware that the portion of the chick's allantois immediately beneath this membrane is concerned with respiration, having been designated as the "avian placenta" by some, and that covering it with petrolatum effectively sets up a state of at least partial asphyxia.

Barcroft and Barron [23] discussed the two divergent conceptions relating to development of behavior. They stated that "these two views appear both to be partially true" (page 477), but that "local mechanisms do appear to become segregated out from the total response in the sense implied by Coghill in his account of the development of behavior in Amblystoma" (page 500). We agree that the theory as related to mam-

22. Kuo, Z. Y.: Studies in the Physiology of the Embryonic Nervous System: II. Experimental Evidence on the Controversy over the Reflex Theory in Development, J. Comp. Neurol. **70**:437, 1939.

23. Barcroft, J., and Barron, D. H.: The Development of Behavior in Foetal Sheep, J. Comp. Neurol. **70**:477, 1939.

mals is based on observations true enough in themselves, but incomplete. Sufficient attention has not been paid to anesthesia and effects of anoxemia. Prior to the time when one of us (W. F. W.) joined the Cambridge group, late in 1935, it had been impossible to observe local responses in young sheep fetuses. The reason for this seemed to be at least twofold. Ethyl carbamate had been employed as a general anesthetic, and no stress was laid on the necessity of making observations at the moment of incising the uterus. By shifting to durocaine (a pseudohypobaric solution of procaine hydrochloride), used as a spinal anesthetic, and by employing a more rapid approach to the specimens it was possible, in the small amount of material available for study, to observe localized responses in sheep fetuses about the thirty-fourth or thirty-fifth day of gestation. Most of the experiments on which the recent report of Barcroft and Barron was based appear to have been performed on older specimens, in fact, mostly on specimens considerably more advanced in development than the oldest cat embryos of our present series. Their data constitute a valuable contribution to the subject when considered in the light of conditions obtaining during experiments. The Cambridge group have recognized the fact that the oxygen content of fetal blood drops markedly on opening the uterus.[16b] May it not be that in the sheep, as well as in the cat, local responses are thrown out and mass reactions increased by this partial anoxemia?[24]

CONCLUSIONS

The earliest somatic activities of which cat embryos are capable made their appearance about twenty-three days after insemination. They were simple reflex responses to stimulation of the forelimbs or head.

Throughout the following ten days of the gestation period additional simple responses manifested themselves. Hand in hand with the appearance of simple movements there was progressive integration of the activities already laid down.

The nature of early fetal behavior varied with changes in the respiratory metabolism of the fetuses. When deficiency in oxygenation or elevation of carbon dioxide became effective, the fetuses at first became more irritable to light tactile or pressure stimuli and the individuality of responses was clearly defined. However, with further anoxemia the individual movements became depressed, some, especially movements of appendicular muscles, being lost entirely; irritability decreased, and spontaneous movements of a fully integrated mass reaction resulted. Under conditions of anoxemia stimulation of the fetuses resulted in mass

24. The reports of Kuo and of Barcroft and Barron appeared after the present article had been written. The last two paragraphs of the preceding section were added at that time.

movements. The greater the asphyxia, the more tonic and sustained were these mass responses. Severe asphyxia, however, ultimately led to breakdown of the total response and to depression of all activities.

Rhythmicity of certain movements, especially of the muscles to be employed in respiration after birth, appeared in fetuses about 30 to 31 days old under conditions of partial anoxemia. With further increase in the carbon dioxide level or decrease of the oxygen in air breathed by decerebrate cats, it was possible to bring about participation in these respiratory-like rhythms of progressively more muscles until tonic, dyspneic gasps alone occurred.

It is concluded that behavior develops by a process of integration of unit reflexes, which occurs with progressive growth of connections within the central nervous system. Experimental procedures usually disturb respiratory metabolic conditions so quickly that the individual movements are destroyed before adequate stimuli can be brought into play to elicit them, the mass reaction, i. e., Coghill's total pattern, being the only form of behavior remaining during partial anoxemia.

A CLINICAL STUDY OF ANXIETY ATTACKS

HARRY L. KOZOL, M.D.*
BALTIMORE

Acute attacks of anxiety were the outstanding feature of the 48 cases on which this study is based. The conditions in these cases were diagnosed variously as "anxiety neurosis," "anxiety state" and "anxiety-tension state." It is believed that a presentation of the experience and point of view of one particular clinic may be of interest to those dealing with anxiety problems. References to the literature are omitted for the sake of brevity.

MATERIAL

The 48 cases on which this study is based were selected at random as typical examples of anxiety attacks seen in this clinic. They were not selected as textbook or paradigm cases, and it is agreed by members of the staff that they fairly represent the clinical material. This paper does not treat of the commonly recognized anxieties of everyday life and of those psychiatric states, such as depressions, in which the anxiety aspect is not the outstanding feature of the clinical picture. Nor does it treat of cases in which the anxiety state seems to be secondary to gross organic disturbances, such as cardiac disorders.

Of the 48 patients, 27 were males and 21 were females.

The age at onset of the attacks was under 30 in 33 cases. One is impressed with the comparatively early age at which anxiety attacks appear. Thus, 17 of these 33 patients had the onset not later than at the age of 21. In 2, the onset was at 14, and in 3, at 16. The highest age of onset in this group was 40, the attacks developing in 3 patients at that time.

The average length of time spent in the hospital was two months. The longest single stay was eleven months, and the next longest was five months. Sixteen patients stayed only one month, and 4 patients stayed only a few days. The patients who left early rejected a psychiatric approach to their difficulties and in general showed an extraordinary paucity of insight.

CLINICAL ASPECTS

In each of the cases consideration of the total clinical picture provided the perspective for a balancing of the multiplicity of relevant features which appeared to be present in most of them.

This mode of approach may be briefly illustrated by the report of the following case. It will be noted that the approach does not differ materially from any other "common sense" approach to psychiatric problems.

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* Fellow of the Rockefeller Foundation.

From the Phipps Psychiatric Clinic of the Johns Hopkins Hospital. This article is based on a paper read at the celebration of the twenty-fifth anniversary of the founding of the clinic.

A business man aged 35, a "socialite," entered the clinic after nearly two years of anxiety attacks and related somatic disturbances. On admission he complained: "It's exhaustion. I get in cold sweats. Suddenly I thought I was going to faint. I got paralyzed with panic."

He was a self-indulgent, dependent person and had been raised by an overprotective, worrisome mother, who had herself received psychiatric treatment for anxiety attacks. He disappointed his family by failing to get into college, despite heroic tutoring. In 1922, he entered his father's large industrial plant. There his work and efforts were unsatisfactory to his father, who constantly criticized him. His father resented the patient's tendency to take advantage of the fact that his father was the "boss." He repeatedly told the patient he was not worth his salary and was the object of paternal charity, and dared him to leave the position and do better elsewhere. The patient recognized the probable truth of all these remarks and felt increasingly inadequate and dependent.

In 1933, he married a wealthy divorcée, somewhat his junior. She came to him with an income of $20,000 a year and an entourage of 4 children, ranging in age from 7 to 13. Marriage brought him few of the usual responsibilities associated with such a venture. Nor did he hesitate to take full advantage of the pleasures his wife's large income made possible.

In the summer of 1934 his wife became pregnant. Despite the size of her income, he ruminated that this child would be his responsibility, the first real responsibility he had ever had. He grew increasingly tense over this and felt chronically uneasy in contemplation of becoming a father. Meanwhile the differences with his father grew more acute; he dreaded going to work and being exposed to humiliation and criticism.

In April 1935, two days after the birth of his child, he had his first anxiety attack. On the day of the new arrival he had celebrated in a conventional fashion by drinking heavily. The next day found him back in his office contemplating his new responsibility and his unhappy occupational situation. Suddenly he felt faint and fearful. He described his experience thus: "It was as though the blood were draining out of my head. I wanted air. I was afraid I would collapse. I felt breathless. It was a feeling as if I were going to die. I was completely puzzled and damned well scared."

He at once put himself in the hands of an internist, who hospitalized him for a week and recommended a three months' vacation. On his father's insistence, he reluctantly returned to work in a few weeks. In succeeding months he was tense and chronically apprehensive. He said: "My stomach felt tied up muscularly, with a lump in the middle of it. The feeling would come on in the office. I didn't have confidence to drive home for fear of fainting or something."

Two months after the first anxiety attack, a second acute attack appeared while he was driving through a traffic tunnel on a very hot day to a routine engagement. He was suddenly overwhelmed by fear, had a tremendous urge to escape from the confining space of the tunnel and wondered if he would collapse, cause an accident and get killed.

In the following months the tension and chronic vague apprehensiveness continued. There were constant epigastric tightness and discomfort, loss of appetite and often anorexia. There were frequent bouts of diarrhea, each following an altercation with his father about his work.

Until admission to the clinic in December 1936, he had frequent acute states of fear with palpitation, breathlessness and dizziness when in elevators, trains, movie houses and crowds. At times he specifically feared he might die.

Examination.—On admission to the clinic he was obviously tense and was mainly preoccupied with his attacks and bodily complaints. Physically he was asthenic. His pupils were dilated; his mouth was dry, and the pulse rate was 64. No pharmacodynamic tests of autonomic functions were made.

Course.—During his stay in the clinic he was chronically tense and apprehensive, particularly about his health. His pulse rate fluctuated moderately between 70 and 100. There was no diarrhea or constipation; sleep was good.

The first acute anxiety attack in this clinic appeared ten days after his wife's first visit. He suddenly felt acutely fearful of some vague personal catastrophe. There were acute bodily discomfort with palpitation (and a pulse rate of 110), breathlessness and a sinking feeling in the epigastrium. Several other acute attacks appeared, in one of which he feared that he might lose his mind and kill himself. Most of the attacks came in a setting of rising tension as discussions of leaving his father's business came up.

Treatment was administered along the following lines:

1. Demonstration that there was nothing in his physical status which should concern him.

2. Scrutiny of his past history to find and demonstrate logical and chronologic relationships between certain situations and his development of states of tension and acute attacks of fear.

3. Discussion of personal tendencies to cross bridges before he came to them, to shrink from hardships and responsibilities and to indulge himself.

4. Discussion of life goals and objectives apart from those dictated by his family or social milieu.

5. A specific plan to give up the position with his father and to amplify a hobby into a definite occupation.

In all the clinical pictures presented by the patients studied circumscribed attacks were present. Forty-one of the patients spontaneously used the word "fear" in describing how they felt, and of these 31 specified the fear of death. Examples of the patients' remarks follow:

1. "The way a man would feel if he had just fallen off a tall building, terrified—nothing can be done; you are finished—just waiting to hit."

2. "I get the jitters—scared more than anything else."

3. "Fear is the chief thing."

4. "I'm afraid my heart is going to stop."

None of the patients used the word "anxiety" to describe their feeling during the attacks. Two who had had previous psychiatric contacts offered a diagnosis of "anxiety neurosis." Of the 7 patients who did not spontaneously use the word "fear" in describing their attacks, 5 described an urgent impulse to get away from the immediate environment, behavior which is commonly recognized as associated with fear reactions.

Returning to the 41 patients who spontaneously spoke of experiencing "fear" in their attacks, it is important to note that in each case the fear related to an imminent personal catastrophe of the patient himself. It was fear of an event, of something about to happen to the patient. In none of the cases did the fear involve an object or the

welfare of some other person. Thirteen stated specifically that fear of death was present in the first attack. Three had fear of insanity in the first attack. In over half the others vague fear was present in the first attack and only later became definitely focused on death. A few patients expressed fear of insanity as well as of death. When the mode of expected death was specified, as in a few cases, it was usually cardiac—perhaps because such deaths are popularly thought of as sudden. Although both the respiratory system and the gastrointestinal tract figured in the attacks of some patients, these were not pointed to as probable sources of sudden death.

Hypochondriacal features were present in about one third of the cases. The chronic anxiety in most cases concerned the heart. One patient feared a tumor of the brain, and one feared she might become paralyzed. Urgent impulsion to escape from the immediate environment was present in over half the cases.

SOMATIC CONSIDERATIONS

In all but 1 case the patients emphasized disturbing bodily states. Over half the patients did not show the full classic picture of physical symptoms described in anxiety attacks, namely: palpitation, choking, dry mouth, cold sweat, numbness of the extremities, epigastric discomfort and urge to defecate. In the majority of cases, however, the complaints tended in such direction, the most common ones being palpitation, choking and urge to defecate. In 1 case the symptoms were limited to tightness of the back of the neck, and in another to similar tightness of the neck and heaviness of the eyes.

Manifestations of disturbances of the autonomic nervous system were not uniform. In most of the patients' somatic reactions there was an admixture of sympathetic and parasympathetic phenomena. In few cases was there a relatively "pure" sympathetic or parasympathetic picture. On the whole, however, there was a predominance of sympathetic manifestations. One is impressed, in general, with the fact that it is the whole person reacting rather than an arbitrarily defined part.

Pharmacologic studies of function of the autonomic nervous system were not systematically carried out. In this study, therefore, no comment can be made on the views of Misch, on the one hand, and Pellacanni, on the other, but it is believed that the anxiety state is not specifically related to either sympathetic or parasympathetic tonic dysfunction.

This study did not reveal why the pattern of physiologic reaction should be what it is in each case, but in a few susceptibility to palpitation, extrasystoles and gastric disturbance seemed to typify the pattern of attack. The attacks tended to recur in the same pattern in each individual case.

INSIGHT

Only 2 patients showed spontaneous awareness (insight) into seemingly obvious connections between the attacks and difficulties in their personal life situations! Several patients actually denied any connection between the attacks and situational difficulties, even when this connection seemed obvious. In fact, when these patients are reviewed as a group, one is struck with the lack of insight into the possible relationship between the attacks of anxiety and apparently obvious situations. It is suggested that this poverty of insight may have disposed to the summation of unappreciated stresses into the volcanic upheavals of the acute attacks, as well as to have sensitized the patient to relatively trivial difficulties.

ETIOLOGIC FACTORS

In scrutinizing the patients' life situations, potentially disturbing factors appeared in all the cases; in most there was a multiplicity of such factors. On the whole, few of the patients seemed to recognize explicitly the existence of these situations and their disequilibrating influences.

Insecurity was the most common single feature of these situations. This insecurity often related to matters of affection, sex and marriage. In a few cases the insecurity related to health, and in about an equal number it related to economic status. Uncertainty and suspense were common elements.

Sex factors of various sorts played a role in four fifths of the cases, and in nearly half the cases such factors were of primary importance in the situational stresses of the patients. Sexual frustration was present in only a very small number and a feeling of guilt in only 2. Sex factors operated in many different ways. One example may be given here.

A boy aged 16 with severe attacks in which he feared to die of heart trouble had absorbed all his mother's attention for two years. His father was dead. In the clinic it was noted that anxiety attacks occurred after dreams of intercourse with his mother. It soon appeared that she was interested in a prospective second husband, toward whom the patient had not recognized any hostility.

It should be added in this discussion of situations that threats of frustration of ambition were nearly as common and important as sexual factors. It should be repeated, also, that in any particular case there was usually a combination of factors such as those just described.

In the early background of many of the patients one item stood out. That was overconcern about the patient's bodily health on the part of oversolicitous mothers.

In the attempt to find personality traits which might be characteristic of this group of patients, the following items are offered as suggestive of the outstanding tendencies: egotism, self centeredness, sensitiveness

to the opinions of others, ambitiousness, aggressiveness, intensity, apprehensiveness and anticipatory trends. Over one third of the patients were body conscious. It should be added that there was, however, considerable variability of personality traits, some patients showing features exactly the reverse of those just mentioned.

In only 5 of the 48 cases was there no evidence of personality imbalance.

When the personality was heavily burdened with liabilities, particularly when there was great sensitivity to the opinions of others with efforts to live up to certain standards and attain certain goals, there seemed to be an increased vulnerability, manifested by the development of anxiety attacks in the face of situations which are not ordinarily looked on as formidable. In my cases such situations involved simple school and occupational responsibilities.

The possible role of heredity in these cases arises when one considers that in only 4 cases was there complete absence of personality imbalance in other members of the family. Two of these patients also showed no personality imbalances. In the heredity of three fourths of my patients there were definite psychiatric disorders, many of which were psychiatrically treated, some in this clinic. In about a third of the cases the personality disorders in the line of direct ancestry were anxiety attacks.

TREATMENT

Treatment in the individual case began on admission, with a search for the actual facts. In this the patient played more than the part of a passive onlooker. There was mutual distributive scrutiny of the facts in each case. This presented opportunities for the patient to learn about himself and about the nature of the situational stresses to which he had been subjected. It also presented opportunities for him to discover relationships between his attacks and more general difficulties from which he shrank or sought escape. This tended also to bring considerations of the patient's assets as well as limitations into the foreground. Responsibility was balanced between the patient and his situational difficulties. The balanced consideration of the multiplicity of factors in each case prevented unifocal emphasis on the patient or situation alone. The total picture, with its many interrelationships of items, was constantly kept in mind. When possible, practical help was given in changing the situation.

A young woman who had been through difficult labor experienced attacks of anxiety when about to resume marital relations with her husband. She was ignorant of contraception and dreaded another pregnancy, yet saw no relation between those factors and the fact that her anxiety came only at bedtime. She

was given explicit instruction about birth control; insight and confidence appeared. In the two years that have elapsed, during which she has not been pregnant, she has had no acute anxiety attacks.

Psychoanalysis was not systematically carried out in more than 1 case. Psychoanalytic formulations were used as part of an eclectic approach whenever they seemed particularly relevant. In this respect, one could not help being impressed by the finding of a few instances of frustrated sexual experience and of deep hostility.

RESULTS

The results of treatment were difficult to evaluate. In many of the cases attacks were observed in the clinic. Improvement through the mere fact of entering the clinic was not striking, in contrast to what one often sees in patients with paranoid panic states. Many of the patients seemed to accept assurance that the attacks did not involve any physical danger. Development of insight was meager on the whole. In fact, it seems that this group of persons was rather resistant to the development of psychogenic formulations of their difficulties. An example of this is offered by a patient who was intensively studied and treated in this clinic for five months. After discharge he reported marked improvement. Some months later the patient told his particular clinic physician that in his opinion what had been most responsible for the improvement was the doctor's recommendation that he be sent to a state hospital if he did not get better promptly.

In the few cases in which development of insight stood out in contrast to that of the other patients it cannot be stated that there was dramatically prompt improvement, but there did seem to be development of confidence on the part of the patient toward his handling of future difficulties.

At the time of discharge from the hospital few of the patients were having attacks which were as severe as those at the time of admission. In some of the cases in which the attacks were as severe, the patients faced a return to the situations which seemed to be largely responsible for the attacks. An instance follows:

In the case of a young Catholic woman the attacks, which came only at bedtime and which seemed related to fear of sinning through contraception, stopped suddenly two years after her discharge from the hospital, when she became pregnant, and recurred when the pregnancy ended and contraception was again insisted on by her husband.

Twenty-eight of the patients have been followed after their discharge from the clinic. One has been observed for twenty-three years and another for twenty years. In most of the cases definite improvement has come in the course of time, but absolute freedom from attacks was

attained by few. On the whole, however, the attacks were milder and less frequent and were taken less seriously by the patients. It seems that the tendency to the development of anxiety attacks is a deeply ingrained constituent of the personality, to be looked on perhaps as a hair trigger escape mechanism.

Changes in situation wrought by time and circumstance seemed, on the whole, to be significant in the alleviation of the condition. Even marked constitutional liabilities gave way to favorable situational changes. It is difficult to delimit the actual effects of the treatment in the clinic. On the whole, however, one is not impressed with any widespread, phenomenal successes. Each case was a strictly individual matter, and the outcome, like the cause, was dependent on a multiplicity of factors. One former patient, a nurse, who was treated in the clinic twenty years ago, was recently interviewed. She is enthusiastically appreciative of what the clinic did for her. She continues to have an occasional severe anxiety attack in the face of new responsibilities, but says she learned in the clinic to minimize the seriousness of the attacks; this point of view has made it possible for her to make a happy and successful adjustment.

DEFINITION OF "ANXIETY"

No attempt is made here to define the word "anxiety." As between individual patients, there are apparently great differences in quality and intensity of experience. It is thought that "fear" in greater or less degree is a common and essential component. In the individual case there may enter also features of uncertainty or suspense. A definition general enough to fit the diversity and variety of manifestations in these cases would have to be so broad as to be essentially valueless in respect to the individual case.

SUMMARY

Forty-eight cases in which the occurrence of acute anxiety attacks was the outstanding clinical feature are reviewed.

The attacks tend to have their onset rather early in life.

In the attack the behavior of the patient is similar to familiarly recognized reactions in the presence of danger.

No attempt is made in this paper in the direction of refinement of definition between the specific words "anxiety" and "fear."

Somatic reactions were mainly: palpitation, choking and urge to defecate. Few patients showed the full classic picture described in the literature. Manifestations of autonomic nervous disorders usually involved the participation of both sympathetic and parasympathetic divisions, with some predominance of the former.

The attacks appeared in a background of tension or chronic vague apprehension. Yet they were described by the patients as something new, not as mere exacerbations of the chronic worries and tensions to which most people are subject.

Poverty of insight regarding the relation between situational stresses and the occurrence of attacks was striking.

Insecurities relating to a wide range of human interests seem to stand out in the situational background.

Heredity is significant in most cases.

The personality tends toward egocentricity, sensitiveness to the opinions of others, a tendency to cross bridges before they are reached, aggressiveness, intensity, ambitiousness and apprehensiveness.

In treatment, an eclectic point of view with a totality of perspective went hand in hand with intense scrutiny of specific details.

Results of treatment were not dramatic. In most of the cases the attacks subsided while the patients were in the hospital. Twenty-eight of the patients have been followed since discharge, one for twenty-three years. In all, improvement came with time, but few attained absolute freedom from attacks.

Dr. Richard S. Lyman gave helpful criticisms and suggestions.

CONGENITAL DEMYELINATING ENCEPHALOPATHY

ROLAND P. MACKAY, M.D.
CHICAGO

The term diffuse sclerosis has been used to cover a wide variety of pathologic conditions. Pelizaeus-Merzbacher "disease," arising late in childhood and apparently familial, is characterized by diffuse but incomplete demyelination, followed by slowly progressive gliosis.[1] Schilder's [2] so-called encephalitis periaxialis diffusa, on the other hand, occurs in infancy or early childhood, is not familial and runs a much more rapid course. The demyelination is more acute and complete and the gliosis less profound, being proportional to the chronicity of the process. A third type was described by Krabbe,[3] which resembles Schilder's disease but is familial and leads to more marked gliosis. The literature contains the reports of many cases, each differing in some respect from the others, and the task of bringing order out of chaos seems insuperable. Neubürger and Schob [4] divided "diffuse scleroses" into three groups: (*a*) blastomatous, (*b*) exogenous-inflammatory and (*c*) endogenous-degenerative. The first of these types should probably be excluded as being neoplastic. Since no one has settled the dispute as to what constitutes inflammation in the brain, the separation of the exogenous-inflammatory from the endogenous-degenerative forms is at present pathologically impossible.

From the Laboratory of Neurohistology, Illinois State Psychiatric Institute, Department of Public Welfare.

Read at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 6, 1939.

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2. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose: Ueber Encephalitis periaxialis diffusa, Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912; Zur Frage der Encephalitis periaxialis diffusa (sogenannte diffuse Sklerose), ibid. **15**:359, 1913.

3. Krabbe, K.: A New Familial, Infantile Form of Diffuse Brain-Sclerosis, Brain **39**:74, 1916.

4. Neubürger, K.: Histologisches zur Frage der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:336, 1921. Schob, F.: Progressiver familiärer Schwund des Hemisphärenmarkes (Familiäre diffuse Sklerose bzw. Leukodystrophia cerebri progressiva hereditaria—Bielschowsky), in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pt. 7, pp. 978-984.

If, according to Globus and Strauss,[5] one confines attention to cases in which the changes are restricted to myelinated fibers and are clearly degenerative, a unified pathologic group can be delimited. The chief characteristic of this group is demyelination, not sclerosis. The process is therefore a demyelinating encephalopathy in which gliosis is a secondary, and not an essential, feature, since in some cases the glia itself is damaged and scarcely proliferates.

Relatively little attention has been paid to congenital forms of this demyelinating encephalopathy; Virchow[6] spoke of encephalitis congenita, as did Seitz.[7] Later Wohlwill[8] described cases in which the white matter, with or without the cortex, might be damaged at or before birth by a degenerative process. He expressed the belief that trauma plays at least some part in this process. In the following 3 cases the clinical data at hand, although meager, seem to indicate that the patients were affected from birth. In all 3 cases demyelination led to destruction of axis-cylinders, the glia being partially damaged, and in 1 case the process came to an end long before the patient's death and was therefore not progressive.

REPORT OF CASES

CASE 1.—*Clinical History.*—D. D., a first-born, white boy aged 2 years, was admitted to the Dixon State Hospital, Dixon, Ill., on Aug. 22, 1938. The parents were normal; a younger sister was in good health, but no further family history was obtained. The patient's first teeth appeared at the seventh month; he had never sat up, walked or talked. At 4 months of age he had bronchopneumonia, and at about the same time began to have convulsions, which continued at frequent intervals until his death. From time to time he had "peculiar sores" on his head, the nature of which was unknown.

Examination.—On admission the child had a mental age of 3 months and an intelligence quotient of 13. He was microcephalic, had internal strabismus of the left eye and was spastic in all extremities.

Course.—About two weeks after admission the patient contracted bacillary dysentery, with high fever and cyanosis. He died on September 21.

Necropsy.—There were lobar pneumonia and bacillary dysentery, although no bacteriologic data were available. The brain, fixed in solution of formaldehyde, was sent for examination to the laboratory of neurohistology of the Illinois State Psychiatric Institute.

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5. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy, Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

6. Virchow, R.: Congenitale Encephalitis und Myelitis, Virchows Arch. f. path. Anat. **38**:129, 1867; Encephalitis congenita, Berl. klin. Wchnschr. **20**:705 (Nov. 12) 1883.

7. Seitz, L.: Ueber die durch intrauterine Gehirnhämorrhagien entstandenen Gehirndefekte und die Encephalitis congenita, Arch. f. Gynäk. **83**:701, 1907.

8. Wohlwill, F.: Zur Frage der sogenannten Encephalitis congenita (Virchow): II. Ueber schwerere cerebrale Destructionsprozesse bei Neugeborenen und kleinen Kindern, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:360, 1921.

Gross Appearance of the Brain: The brain was fairly well developed externally but was very small, measuring 10.5 cm. in the interparietal and 12 in the fronto-occipital diameter. In frontal sections the white matter was uniformly reduced in amount, especially in the temporal lobes. The corpus callosum was a thin, translucent membrane, which had been torn previously. The internal capsule was greatly reduced. The remaining white matter lay immediately beneath the cortex and near the ventricles, but was frequently destroyed in these places. There were some compensatory dilatation of the ventricles and infolding of the cortex. The basal ganglia were essentially normal, while the cerebellum, pons and medulla

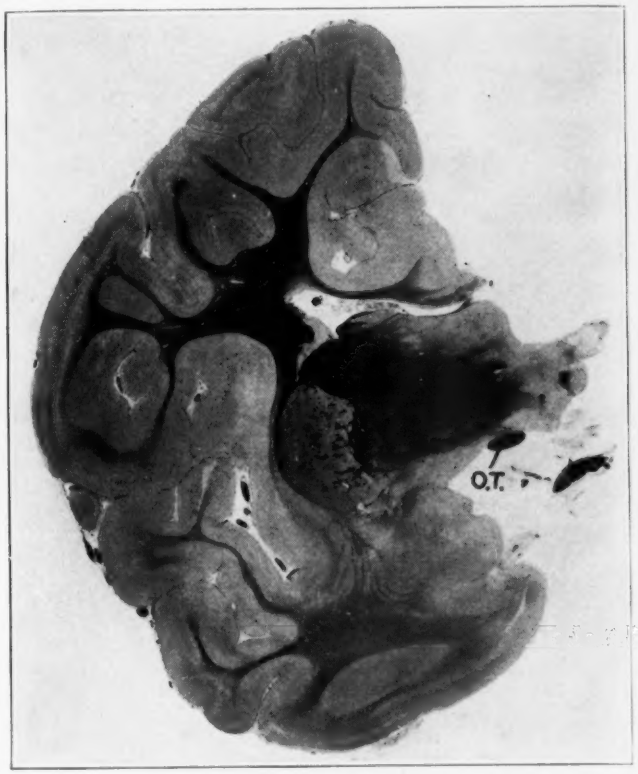

Fig. 1 (case 1).—Frontal section of the right cerebral hemisphere, stained by the Weil method for myelin sheaths. Note the extensive demyelination and shrinkage of the white matter, including the corpus callosum; the infolding of the cortex; the partial demyelination of the cortex, especially in the gyrus cinguli, the island of Reil and the hippocampus, and the relative preservation of the thalamus, lenticular nucleus and optic tract (*O. T.*). Arcuate fibers are generally involved. The area of subependymal gliosis around the ventricle is unstained. × 1½.

were small but of usual proportions. The consistency of the whole brain was normal for formaldehyde-fixed specimens.

Microscopic Appearance: Myelin sheath stains made by the Weil method confirmed the observations made on the gross specimen (fig. 1). No myelin was

visible over large areas of the centrum semiovale, and, where preserved, the sheaths were often beaded or vacuolated. The arcuate fibers, occasionally preserved, were usually destroyed, and the myelin of the cortex had almost entirely disappeared. Tangential or subpial fibers were not seen. The optic tracts were well preserved. Stains made with sudan III for fat revealed both fat granule cells and free droplets in the areas of degeneration. These were both scattered in the tissues and collected about blood vessels (fig. 2). Davenport stains of the axis-cylinders demonstrated destruction of these elements in proportion to that of the myelin,

Fig. 2 (case 1).—Scattered droplets of fat in degenerating white matter and about blood vessels. Some of the fat is free in the tissues; some is in fat granule cells. Sudan III; × 190.

although not quite to the same degree (fig. 3). A few swollen and beaded axis-cylinders were seen where the myelin was most severely damaged. Glial stains made by the Cajal, Stern, Holzer and phosphotungstic acid-hematoxylin methods revealed some astrocytic gliosis, especially in the region of the arcuate fibers, but in general the glia had been destroyed in proportion to the loss of myelin and axis-cylinders (fig. 4). Astrocytes were undergoing clasmatodendrosis; the oligo-

dendroglia cells were swollen and often ruptured. Holzer and phosphotungstic acid-hematoxylin stains revealed marked periventricular subependymal astrocytic gliosis resembling that seen in syringomyelia (fig. 5). There was a tendency to astrocytic proliferation and hypertrophy in the lower layers of the cortex in some areas. The cortical glia was in general well preserved. Cresyl violet preparations showed practically no disturbance of the cortex or central gray masses. Descending degeneration could be observed in the pyramidal tracts in the pons and spinal cord. Aside from its small size, the cerebellum had undergone no definite changes. No infiltrations were seen anywhere in the brain or its meninges.

Fig. 3 (case 1).—Marked disappearance of axis-cylinders in degenerating white matter and beading of the remaining fibers. Davenport stain for axis-cylinders; × 327.

The clinical data in this case are, unfortunately, few, but available information indicates that the disease was congenital, although bronchopneumonia occurred at the fourth month of life. The process was one of extensive demyelination, which spared in most areas neither the arcuate fibers nor the myelinated fibers of the cortex. Cellular infiltrations were absent. Axis-cylinders and glia were severely affected,

although some gliosis resulted. The process was rapid and progressive until the patient's death, which apparently resulted from an intercurrent infection.

CASE 2.—*Clinical History.*—M. G., a third-born, white boy aged 2 years and 9 months, was admitted to the Dixon State Hospital on June 13, 1938. At that time his mental age was estimated as 3 months and his intelligence quotient as 9. The parents and an older brother and sister were said to be normal. The mother's

Fig. 4 (case 1).—Degenerating astrocytes in affected white matter. The astrocytes at the left (*a*) are in the lower cortical layers and are well preserved. Those at the right (*b*) are in the white matter and show fragmentation and no processes. Cajal's gold-sublimate (gold chloride–mercury bichloride) stain; × 163.

health during pregnancy had been good. Labor occurred at full term and was normal; the child's weight at birth was 7 pounds (3,175 Gm.). He was said to have been sickly during infancy, but the first teeth appeared at the sixth month. He was epileptic, microcephalic and mentally deficient practically from birth; he sat up at the age of 2 years, but never walked or talked. He had generalized spastic paralysis and undescended testes. He died Sept. 4, 1938, at the age of 3 years, having exhibited a high fever for several days, anemia and a cough. The

clinical diagnosis of the cause of death was bacillary dysentery and bronchopneumonia, but no bacteriologic data were available.

Necropsy.—There were marked emaciation, microcephaly, "involvement" of the intestine with enlargement and hyperplasia of the lymph glands throughout the mesentery and terminal bronchopneumonia.

Gross Appearance of the Brain: The formaldehyde-fixed brain was small, weighing only 685 Gm. Externally the brain was normal except for definite microgyria, especially in the occipital lobes, where some of the gyri were less

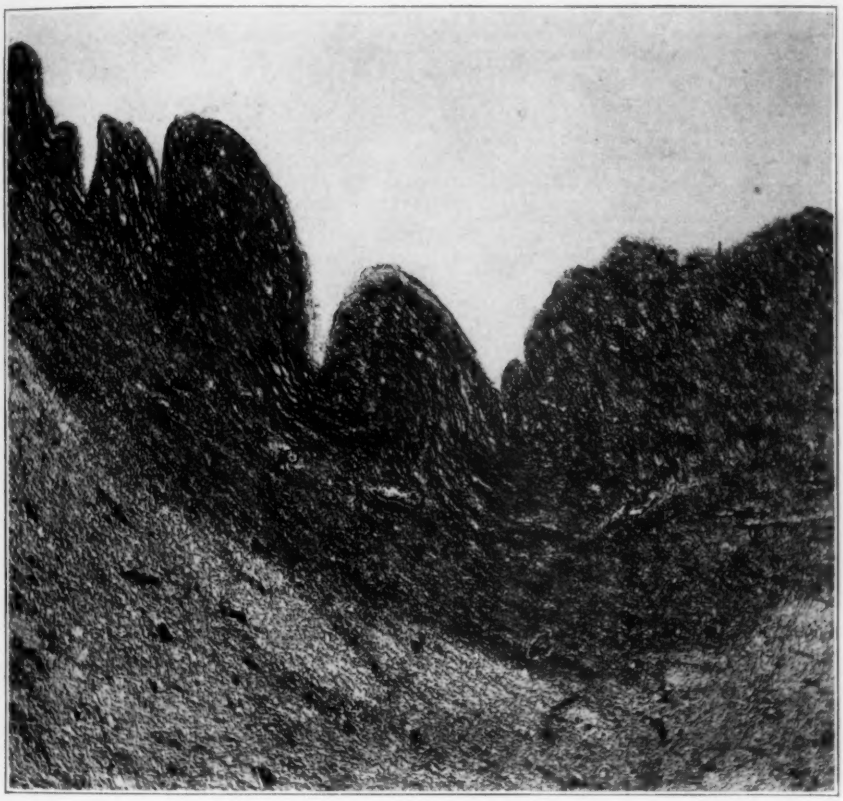

Fig. 5 (case 1).—Periventricular (subependymal) astrocytic gliosis. The gliosis is densely fibrillary and contains few cell bodies. Holzer stain; × about 82.

than 1 mm. in diameter. Frontal sections revealed no particular abnormality except in the occipital lobes, where the areas of microgyria were associated with diminution of the underlying white matter, which consisted of little more than the relatively well preserved arcuate fibers. The cortex had folded in as a result of the loss of white matter, and now occupied much of the interior of the lobes. The microgyria had resulted from this infolding, which had distorted the whole cortex, particularly the calcarine portions. There was no gross abnormality of the basal ganglia, thalamus, pons, medulla or cerebellum.

Microscopic Appearance: Myelin sheath stains revealed marked demyelination of both the white matter and the cortex in the occipital lobes (fig. 6). This condition was more advanced on the right, where practically all myelin had disappeared in the inferior half of the lobe. Smaller areas of demyelination were seen in the left occipital lobe, particularly adjacent to the ventricular horn. In both lobes the arcuate fibers were in part destroyed, and in the calcarine cortex the striae of Gennari were partially demyelinated. The frontal, temporal and parietal lobes, the internal capsule, the corpus callosum, the basal nuclei, the brain stem and the cerebellum contained essentially normal myelin. Fat stains made with sudan III revealed perivascular collections of fat granule cells in the areas involved, but no fat was seen in the tissues. Axis-cylinders were largely destroyed in areas in the occipital lobes in which the myelin was most affected, but in no region had they entirely disappeared (fig. 7). The remaining axis-cylinders were frequently twisted, swollen and beaded. Astrocytic gliosis was advanced in all

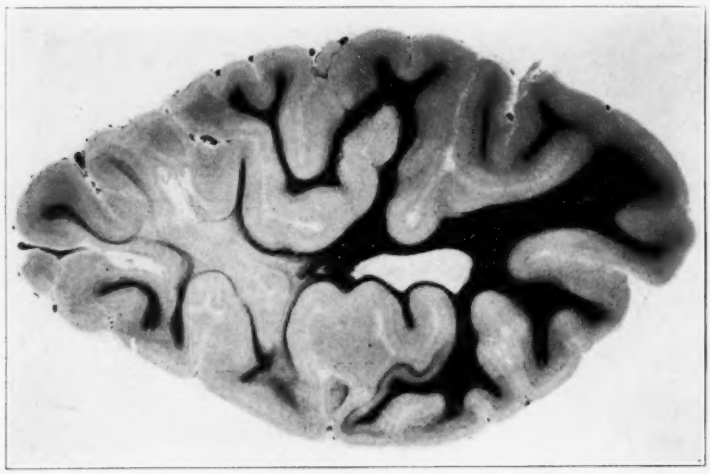

Fig. 6 (case 2).—Frontal section of the right occipital lobe, stained by the Weil method for myelin sheaths. Note the extensive demyelination of the white matter, the cortical infolding, the partial demyelination of the cortex, including portions of the stria Gennari, and the tendency to preservation of arcuate fibers. A layer of subependymal gliosis around the ventricular horn is unstained. × 1½.

degenerated areas, and beneath the ependyma of the occipital horn of the ventricle there was dense proliferation of fibrillary astrocytes, similar to that seen subependymally in case 1. The glia had, however, been partially destroyed where the destruction of myelin was greatest, and appeared more dense where the myelin disease was slight.

Cresyl violet preparations failed to reveal any disease of the ganglion cells of the cortex, basal ganglia or nuclei of the brain stem. This was true even in the cortex overlying the most severely damaged white matter. The cerebellar cortex and central nuclei were likewise normal. No infiltrations were seen anywhere in the brain or its meninges.

This case closely resembles the first in all respects except that the process was practically confined to the occipital lobes. According to

the available evidence, the process seems to have been congenital and nonfamilial. It was essentially one of demyelination without infiltration by hematogenous elements. There was partial destruction of both axis-cylinders and glia, although there was more gliosis than in case 1. Death, again, was due to intercurrent infection—interestingly, of the same sort, bacillary dysentery and pneumonia.

Fig. 7 (case 2).—Marked loss of axis-cylinders in the demyelinated white matter. Note fragmentation and beading of the remaining fibers and the perivascular fat granule cells. Davenport stain for axis-cylinders; × 190.

CASE 3.—*Clinical History.*—M. S., a first-born, white girl aged 10 years, was admitted to the Dixon State Hospital on Dec. 4, 1933. At that time her mental age was 8 months and her intelligence quotient 7. Both parents, 1 younger brother and 4 younger sisters were normal. The patient had been born at the seventh fetal month. The mother had received ether during the long labor; instruments had been used, and the child was asphyxiated and cyanosed after birth. She was also given roentgen treatments, allegedly to reduce "an enlarged thyroid." She had convulsions as an infant and obviously was mentally defective from the first. Her first teeth appeared when she was 7 months of age. She sat up at the end

of the second year, and never walked or talked. She had about three convulsive seizures each year, and was spastic in all extremities. The Wassermann reaction of the blood was negative. A few days before her death she was placed in the infirmary because of slight fever and vomiting, but these symptoms speedily disappeared. She died during the night, presumably during a convulsive seizure. She was 14½ years of age at the time of death, on July 8, 1938.

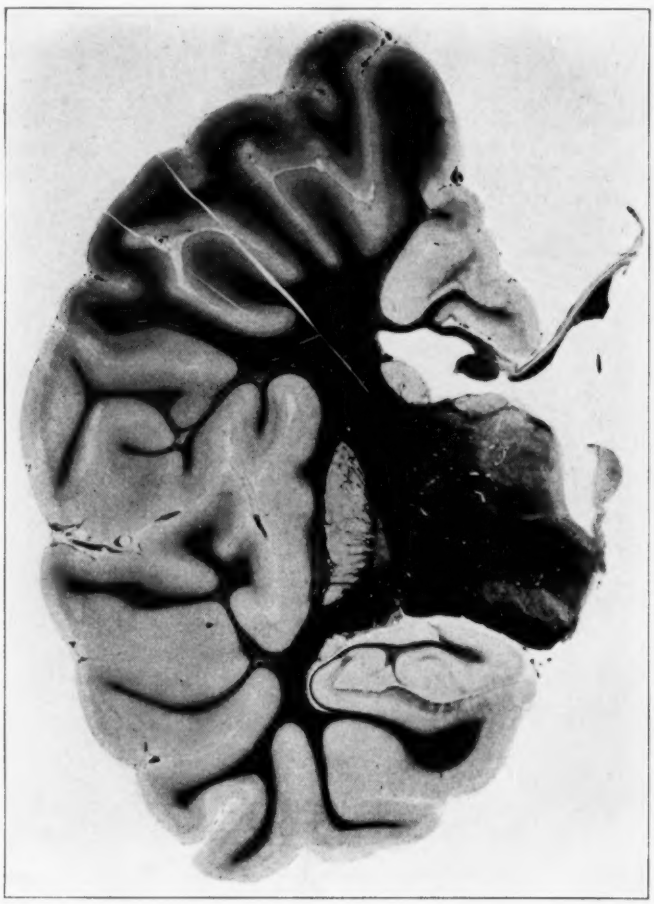

Fig. 8 (case 3).—Frontal section of the left cerebral hemisphere, stained by the Weil method for myelin sheaths. Note the small amount of remaining white matter, the cortical infolding and the relatively few areas of active demyelination. The corpus callosum is severely affected and the entire cortex demyelinated, except in the superior portions. The arcuate fibers, internal capsule, lenticular and caudate nuclei and thalamus are relatively well preserved. × 1½.

Necropsy.—Gross Appearance of the Brain: The formaldehyde-fixed brain was small, weighing only 844 Gm. It was symmetrically developed, but there was cortical atrophy over the frontal and parietal lobes, and the occipital lobes failed to cover

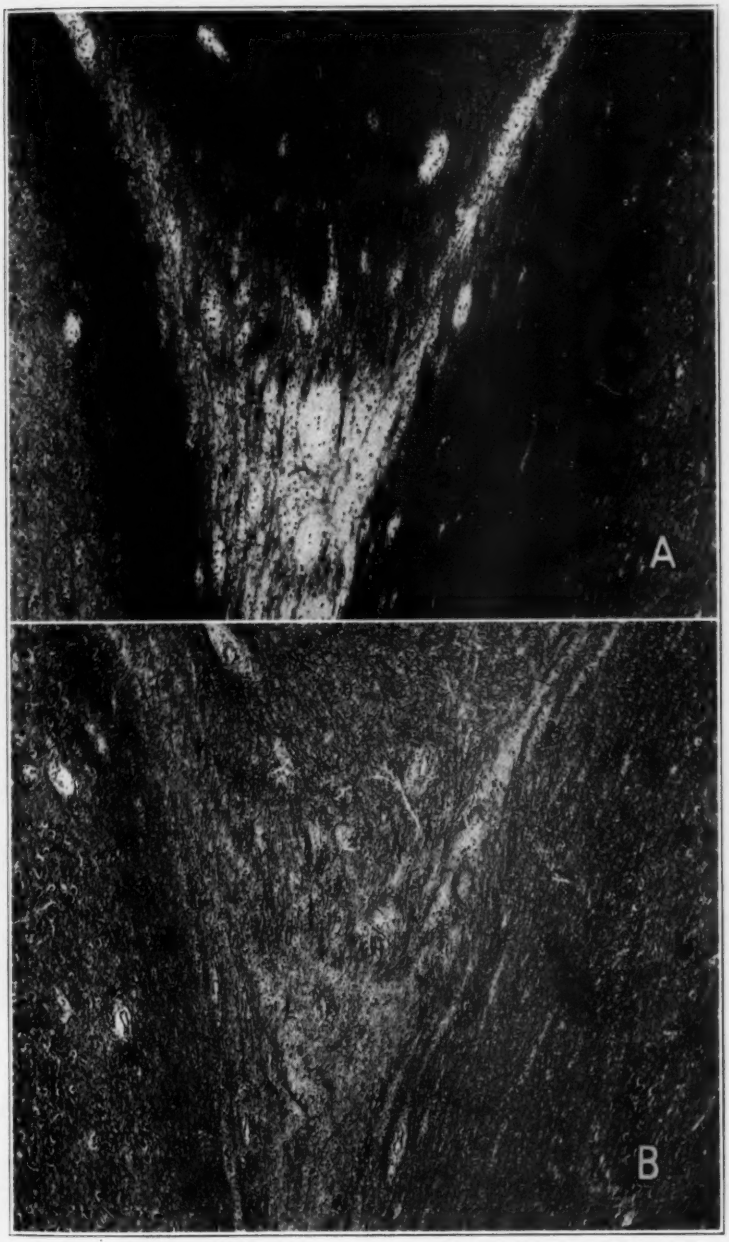

Fig. 9 (case 3).—Destruction of (*A*) myelin sheaths and (*B*) axis-cylinders. Note the equal proportion in which both elements are affected in the same area. *A*, Weil stain for myelin sheaths; *B*, Davenport stain for axis-cylinders; × 70.

the cerebellum. The corpus callosum was thin and almost obliterated in the anterior portion. Cross sections of the hemispheres revealed that the white matter had almost entirely disappeared and had been replaced by folding in of the cortex. The sulci dipped in deeply, and the gyri were folded on one another so that the arcuate fibers of adjacent convolutions were pressed together. The cortex and basal ganglia were well preserved and the internal capsule was surprisingly thick, although most of its fibers came from the parasagittal regions. The capsula externa was thin, and the insular cortex lay directly on the putamen. The brain stem and cerebellum were small, but well preserved.

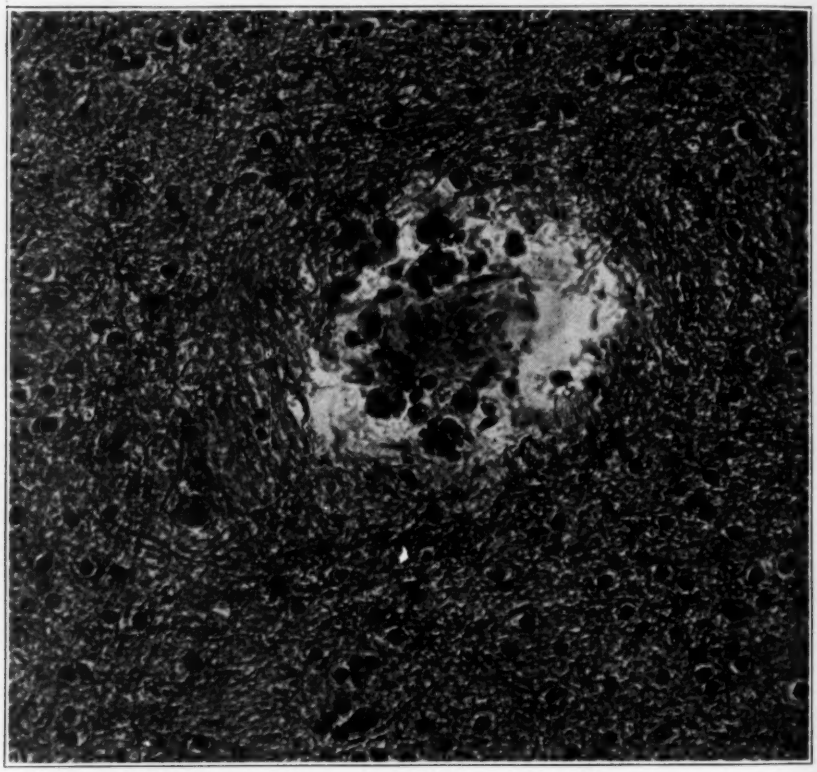

Fig. 10 (case 3).—Fat granule cells in the Virchow-Robin space in degenerating white matter. No fat was seen free in the tissue. Sudan III stain; × 350.

Microscopic Appearance: Myelin sheath stains revealed that the white matter of the cerebral hemispheres consisted chiefly of the fairly well preserved arcuate fibers (fig. 8). The internal capsule was well represented, the fibers coming chiefly from the superior portions of the centrum semiovale, where some white matter persisted. Practically no myelinated fibers were seen in the cortex. The striae of Gennari were partially destroyed. The optic tracts and the myelinated laminas in the thalamus and basal ganglia, as well as these nuclei themselves, were intact. Little degeneration of the descending tracts could be traced into

the medulla, and the myelin of the cerebellum appeared normal. An active process of demyelination was seen in only a few triangular areas in the central portions of the cerebral hemispheres, where distorted and beaded fibers occurred (fig. 9). In these areas, but nowhere else, perivascular collections of fat granule cells were seen (fig. 10), and the axis-cylinders had disappeared in proportion to the destruction of myelin (fig. 9). Remaining axis-cylinders were swollen, kinked and beaded. There was practically no trace of the enormous numbers of nerve fibers which must have been destroyed at some previous time. In spite of the age of the process, little gliosis was seen, except for a minimum in the region of the arcuate fibers. Essentially normal astrocytes were observed in these areas. There was some subependymal gliosis, like that seen in cases 1 and 2. Cresyl violet stains revealed no abnormalities of the ganglion cells anywhere in the brain, except for mild swelling of the cytoplasm and a poor staining quality of the Nissl substance—probably postmortem changes. No infiltrations of hematogenous elements were seen in the brain or its meninges.

In the third case the disease was even more obviously congenital than in the others. The child had endured a dystocic labor, two months prematurely, and had suffered from asphyxia neonatorum. The process was one of demyelination, involving both the white matter and the cortex, with extensive destruction of axis-cylinders and glia. The ganglion cells of the cortex and basal nuclei had been spared; the process had come practically to an end, and the patient had lived, a microcephalic idiot, until nearly 15 years of age.

COMMENT

In all 3 cases microcephaly, idiocy, convulsions and cerebral spastic paralysis were present practically from birth. There is little evidence of a postnatal onset in any of the 3 cases, and in 1 there is a possibility that a premature, prolonged and difficult labor, followed by asphyxia, may have been the etiologic factor. In the first two cases death occurred from intercurrent infections, while the disease, as judged by pathologic features, was still progressing. In the third the process had come practically to an end long before the death of the patient, and the pathologic changes were definitely nonprogressive. In other reported cases of demyelinating encephalopathy in infancy, the condition, as judged by both clinical and pathologic standards, had steadily progressed, and death had occurred at a much earlier age.

In pathologic analysis of these 3 cases, certain features are worthy of emphasis. 1. No infiltration by lymphocytes or other mesodermal elements was seen, and no justification exists for considering the process as inflammatory in the usually accepted sense. 2. The noxious agent, whatever its nature, attacked only myelinated nerve fibers of the cerebral hemispheres, but it involved those in both the white matter and the cortex. Axis-cylinders, though less severely affected, were certainly not preserved. The glia was simultaneously destroyed, although in vary-

ing degrees in the 3 cases. Gliosis was most advanced in the cases of more acute type, and scarcely occurred in the case in which the disease had lasted nearly fifteen years. In all 3 cases gliosis was minimal, a fact consistent with the evidence of glial destruction. This vulnerability of the glia has been mentioned by other authors in instances of demyelinating encephalopathy occurring at more advanced ages.[9] It is unusual, however, and perhaps indicates an unusual etiologic basis in these cases. 3. The presence of rather dense astrocytic gliosis in the subependymal region was noted in all 3 cases and has been reported in other cases, chiefly by Wohlwill.[8] Its significance is not clear, but it is probably not attributable to the direct action of the noxious agent, since that agent tended to destroy glia elsewhere in the white matter. It is more probably related to the transport of tissue debris into the subependymal region.

SUMMARY AND CONCLUSIONS

Three cases of a nonfamilial form of demyelinating encephalopathy are recorded, in each of which the origin was probably congenital. In 2 cases death occurred from intercurrent infection at the ages of 2 and 3 years, respectively, while in the third the patient died in her fifteenth year. All the patients had microcephaly, idiocy, convulsions and cerebral spastic paralysis.

Pathologically, there were widespread demyelination and destruction of axis-cylinders and glia, without mesodermal infiltrations. In 1 case the disease was nonprogressive, and in all 3 the glial reaction was minimal.

The best name for this condition seems to be congenital demyelinating encephalopathy.

9. Jakob, A.: Die diffuse Sklerose, in normale und pathologische Anatomie und Histologie des Grosshirns, Leipzig, Franz Deuticke, 1929, vol. 2, pt. 1, pp. 849-866.

PROBABLE TOPOGRAPHIC RELATIONS OF THE SLEEP-REGULATING CENTER

JOSEPH H. GLOBUS, M.D.
NEW YORK

Sleep as a natural and regular occurrence, more or less rhythmically alternating with the state of wakefulness, is a phenomenon which interests both the physiologist and the clinician. The former is mainly concerned with the underlying factors and the concomitant manifestations of this physiologic state, while the latter seeks an answer to the question whether there exists a regulating center in the brain which maintains a balance between periods of wakefulness and sleep. The neurologist, above all, is bent on identifying the several pathologic forms of reduced wakefulness, protracted deep sleep and allied states, in the hope that in this way signs of focal disturbance in the brain will be disclosed which will aid in circumscribing an area in the brain functioning as a sleep-regulating center.

Early efforts in this direction are credited to Mauthner,[1] who postulated a sleep-regulating center in the gray matter enveloping the third ventricle and aqueduct of Sylvius, as well as that lining the floor of the fourth ventricle, and to von Economo,[2] whose observations on encephalitis lethargica led him to conclude that the rhythmic alternation between normal sleep and wakefulness is a vegetative function, and, as such, has a regulating mechanism in the central nervous system. He placed such a regulating center in the zone of transition between the subthalamus and the mesencephalon. A number of other investigators, notably Troemner,[3] Luksch,[4] Spiegel and Inaba,[5] Adler,[6] Hirsch,[7]

From the Laboratories and the Neurological and Surgical Services of the Mount Sinai Hospital.

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1. Mauthner, L.: Zur Pathologie und Physiologie des Schlafes, Wien. klin. Wchnschr. **3**:445, 1890.

2. von Economo, C.: Sleep: A Problem of Localization, J. Nerv. & Ment. Dis. **71**:249, 1930.

3. Troemner, E.: Schlaffunktion und Schlaforgan, Deutsche Ztschr. f. Nervenh. **105**:191, 1928.

4. Luksch, F.: Ueber das Schlafzentrums, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:83, 1924.

(Footnotes continued on next page)

McKendree and Feinier [8] and Fulton and Bailey,[9] have brought forward clinical and anatomic observations bearing on the views that a regulating center may exist and that its location is probably in the domain of an area in which both the diencephalon and the adjoining part of the mesencephalon are represented.

Ranson [10] brought forward experimental evidence of the existence of a center regulating the alternating sleep-waking rhythm. He placed this center in the hypothalamic portion of the diencephalon, at its posterior end where it merges with the mesencephalon. An experimentally produced lesion in this area provoked in monkeys a state of protracted somnolence. In cats such a state was obtained by a lesion somewhat caudad to that produced in the monkey. But in the cat, in addition to the somnolence, a condition of plasticity was provoked. Thus, a state developed in which somnolence and plasticity were combined so as to simulate the condition seen in patients with a cataleptic form of encephalitis. More recently the same author,[11] with his co-workers, carried out satisfactory experiments on 35 monkeys, 11 of which, when killed, disclosed well demarcated lesions in both lateral hypothalamic areas as far back as the level of the caudal border of the mamillary bodies. Ten of these animals displayed protracted somnolence during life. In another group of 6 animals the lesions were found in both lateral hypothalamic areas, but they did not extend beyond the rostral border of the mamillary bodies. Of these animals only 2 were somnolent. In still another group of 9 animals the bilateral lesions did not extend ventrally far enough to involve the hypothalamic zone. In 5 of these animals somnolence appeared but was of short duration. Finally, in a group of 9 animals the lesions were found either in the thalami or centrally placed. All of these animals recovered from the anesthesia, remained

5. Spiegel, E. A., and Inaba, C.: Zur zentralen Lokalisation von Störungen des Wachzustandes, Klin. Wchnschr. **5**:2408, 1926.

6. Adler, E.: Zur Lokalisation des "Schlafzentrums," Med. Klin. **20**:1321 and 1323, 1924.

7. Hirsch, E.: Zur Pathologie der Schlafzentrum, Deutsche Ztschr. f. Nervenh. **102**:143, 1928.

8. McKendree, C. A., and Feinier, L.: Somnolence: Its Occurrence and Significance in Cerebral Neoplasms, Arch. Neurol. & Psychiat. **17**:44 (Jan.) 1927.

9. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**: 1 and 145, 1929.

10. Ranson, S. W.: Some Functions of the Hypothalamus, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 92.

11. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

alert and active for while, but became somnolent after a lapse of time. This behavior was thought to be due to reactive edema spreading to structures neighboring on the lesions to include the hypothalamic region.

Ranson concluded from his observations that bilateral destruction of the lateral hypothalamic areas leads to somnolence. These are the areas in which stimulation produces combined sympathetic and somatic excitation. It is his belief that descending pathways from sympathetic nuclei in the hypothalamus run caudad in the lateral hypothalamic areas at the level of the mamillary bodies. A part of these descending fibers turn mediad and enter the central gray matter, while a larger part continue downward to the mamillary bodies and mesencephalic tegmentum. It is the concentration of these fibers in the lateral hypothalamic areas which exposes them to excessive stimulation and explains why lesions in such locations block effectively the flow of impulses, causing disturbances in vegetative functions and leading to somnolence.

Recently, 2 patients with protracted somnolence came under observation at the Mount Sinai Hospital, and subsequent postmortem examinations disclosed well circumscribed lesions which, as will be noted from the description of their distribution, bring additional support to the view that a sleep-regulating mechanism with a fairly definite location exists.

REPORT OF CASES

CASE 1.—*History.*—A woman aged 70 was known to have had high blood pressure for about ten years. During the four years preceding admission repeated examinations had revealed maintained hypertension, with the blood pressure readings from 190 to 220 systolic and 100 diastolic. The urine, on repeated examinations, showed traces of albumin, a few casts and a low specific gravity. Her heart was found to be enlarged, and there were irregularities in the pulse, with extrasystoles. From time to time a neurologic examination was said to have disclosed a transient Babinski sign.

During the year preceding admission, and after an attack of influenza, she became subject to recurrent attacks of faintness and dizziness. These episodes occurred more frequently in the wake of a more recent and protracted attack of grip, which lasted two weeks and subsided only a week before the onset of her fatal illness.

On the night before her admission to the hospital she was found in deep sleep, with rather slow and harsh breathing. Suspicion of a serious illness was aroused when it was noted that she could not be awakened, that her hands and feet were unusually cold and that the pulse was slow and faint. In this condition she was brought to the hospital the next morning.

Examination.—The patient was somewhat cyanotic and appeared to be in deep sleep, her breathing being stertorous and of the Cheyne-Stokes type. The heart was moderately enlarged to the left. The pulse rate was 32 per minute and did not change on carotid pressure. The systolic blood pressure was 220 (the diastolic was not recorded). There was pitting edema over both lower extremities. The Babinski sign was obtained bilaterally, while the deep reflexes were depressed.

Laboratory Data.—An electrocardiogram revealed auricular fibrillation with occasional premature contractions and left ventricular preponderance, suggesting hypertrophy of the left ventricle. The spinal fluid was under an initial pressure of 140 mm. of water and contained 3 cells per cubic millimeter. The colloidal gold and Wassermann tests gave normal reactions; the total protein content was 43 mg. per hundred cubic centimeters; the blood sugar was 105 mg. and the urea nitrogen 20 mg. per hundred cubic centimeters. The urine was normal; the hemoglobin content of the blood was 81 per cent.

Course.—The patient continued to sleep. She could be aroused for a brief period, when she would respond to questions, but would soon return to somnolence. It was first thought that she manifested signs of marked cerebral anemia, and on this basis she was given intravenously large doses of theophylline with ethylene diamine. She seemed to respond to this treatment by regaining consciousness more readily and answering questions with greater alertness. But the peculiar

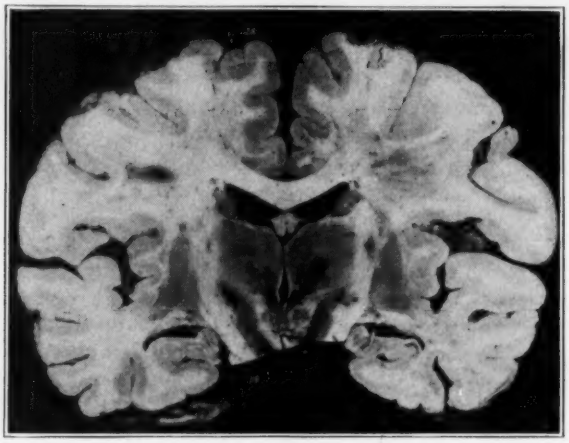

Fig. 1 (case 1).—Gross appearance of a coronal section of the brain, displaying the bilateral symmetric lesions on either side of the third ventricle.

somnolence of the patient suggested to me that the condition simulated protracted sleep, occasioned by the disturbance in the sleep-regulating center. I then suggested that a lesion was present in the periventricular gray matter, probably metastatic in character. The patient, nevertheless, continued to be treated for anoxemia with oxygen and digitalis, but despite these measures she continued to sleep. On the tenth day in the hospital aspiration pneumonia developed, and she died on the twelfth day after admission.

Necropsy Observations.—The large vessels at the base of the brain displayed marked arteriosclerosis. Gross coronal sections of the brain showed two bilaterally symmetrically situated areas of discoloration on either side of the third ventricle (fig. 1). They extended longitudinally from a point at the level of the middle commissure to a point somewhat caudad to the posterior commissure, thus entering the rostral part of the midbrain. The lateral extent of these lesions was studied microscopically.

The diencephalon and the adjacent part of the mesencephalon were cut out en bloc and sectioned serially. Nissl and Weigert stains were employed to demonstrate the alterations in cellular groups and myelinated fiber tracts. Sections at critical levels were selected for the descriptions which follow.

1. Sections at a level somewhat posterior to the massa intermedia showed well defined bilateral lesions, fairly symmetric in outline and extent. They affected mainly the median nuclei of the thalami (fig. 2 *A*), being limited laterally by the internal medullary lamina.

2. Sections at the level of transition of the subthalamic division of the diencephalon into the mesencephalon showed again bilateral lesions, symmetric in location but somewhat less so in outline and extent. Each lesion extended from within the periventricular gray matter laterally, occupying almost the entire zona incerta (fig. 2 *B*).

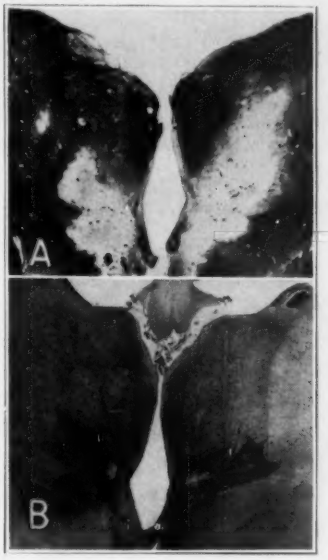

Fig. 2 (case 1).—*A*, section at a level somewhat posterior to the massa intermedia, showing bilateral symmetric lesions affecting the periventricular gray matter but extending into the median nuclei of the thalami. *B*, section at the level of the caudal end of the subthalamus. The lesions are within the periventricular gray matter, extending laterally into the zona incerta.

3. Sections at the level of the anterior part of the quadrigeminal plate showed an area of rarefaction in the commissure of the anterior quadrigeminal bodies and widespread alterations in the periaqueductal gray matter (fig. 3).

In all of these areas there was present a process of softening characterized by the accumulation of compound granular cells (fig. 4), as well as by evidence of disintegration of neurons and their processes. The process was that which is usually encountered in softening following vascular occlusion.

Case 2.—*History.*—A woman aged 55 had undergone a radical mastectomy a week before admission. The operation was carried out with the patient under

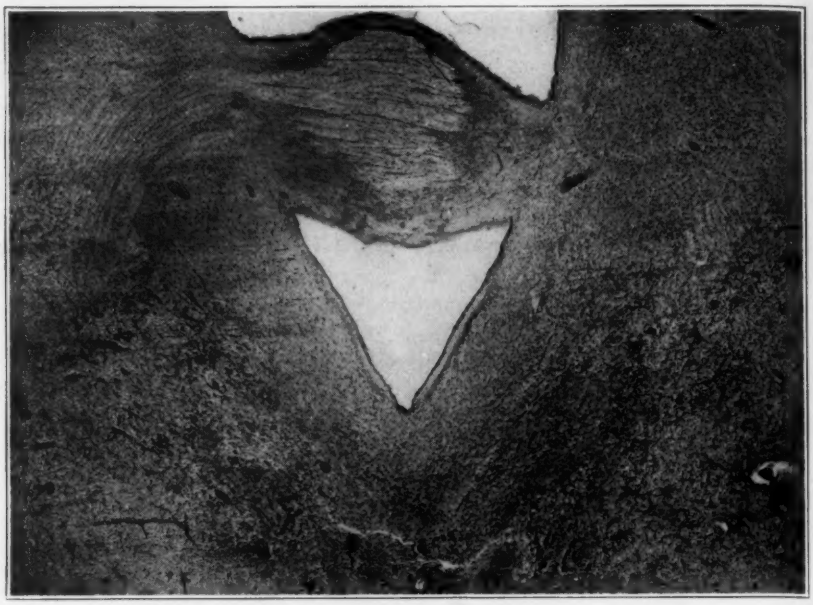

Fig. 3 (case 1).—Section at the level of the anterior quadrigeminal bodies, showing the lesions in the commissure of the anterior quadrigeminal bodies and in the region of the oculomotor nuclei.

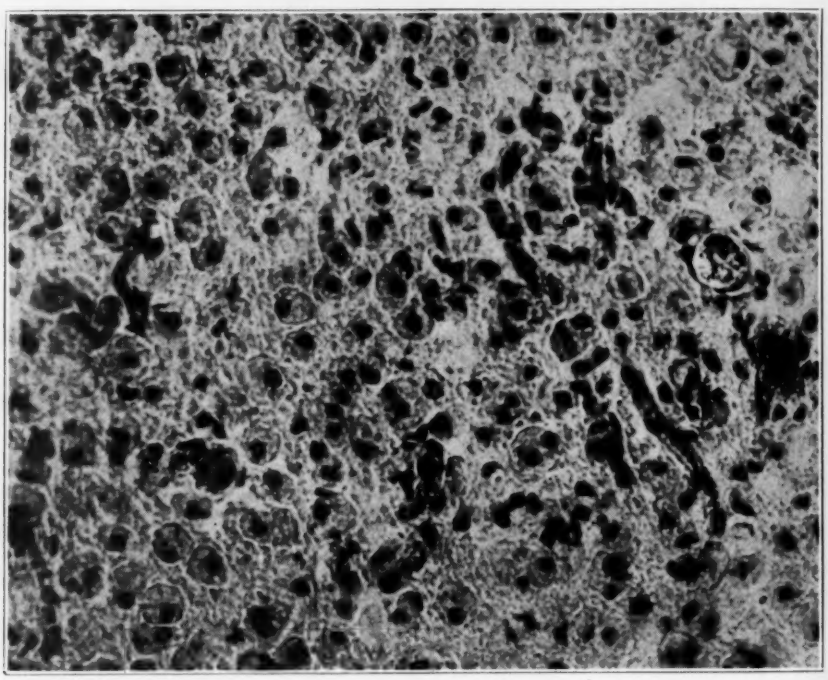

Fig. 4.—Accumulation of macrophages (compound granular cells) in the lesion illustrated in figure 3.

nitrogen monoxide, oxygen and ether anesthesia. On completion of the operation, she did not regain consciousness for over twenty-seven hours; when she subsequently awakened, she continued to be drowsy, gradually becoming stuporous. While in this condition she responded to painful stimuli.

Examination.—Her pupils were small, the left being larger than the right, and the response to light was minimal. There was no paralysis of the limbs; all the deep and superficial reflexes were absent. A lumbar puncture yielded clear cerebrospinal fluid, containing 16 lymphocytes per cubic millimeter. The initial pressure was 85 mm. of water. The urine was normal. Ventriculographic examination showed the posterior horn to be poorly delineated.

Course.—The patient remained comatose; at times she awakened and spoke rationally; at other times she was confused. She died on the sixth day in the hospital, without at any time regaining full wakefulness.

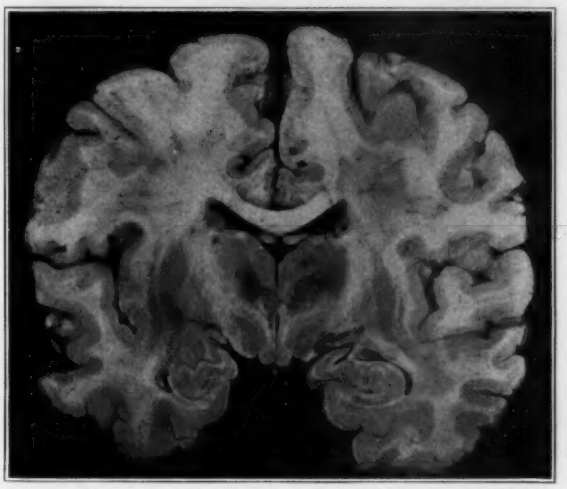

Fig. 5 (case 2).—Gross appearance of a coronal section of the brain, displaying bilateral symmetric lesions bordering on the walls of the lateral ventricle.

Necropsy Observations.—The vessels at the base of the brain showed marked arteriosclerosis. Gross coronal sections of the brain displayed two symmetric lesions bordering on the third ventricle (fig. 5). They extended from the middle commissure to a point slightly caudad to the posterior commissure. Serial sections, studied microscopically, revealed the following lesions:

1. Sections at the level of the massa intermedia and mamillary bodies displayed, as in the previous instance, bilateral symmetric lesions. But here the lesion was seen in the massa intermedia, and from there extended ventrad into the gray matter lining the hypothalamic walls and laterally into the lateral nuclei of the thalamus, sparing completely the median nuclei (fig. 6*A*).

2. Sections at the level of the posterior end of the third ventricle showed that the lesions were symmetric and extended from a small central area in the subthalamus, just above the anterior extremities of the red nuclei, laterally into the lateral nuclei of the thalamus. The lesions here were less symmetric (fig. 6*B*).

3. Sections at the level of the anterior extremity of the red nuclei showed that the lesions were close to the midline and spread out laterally for a short distance in the subthalamic region (fig. 6*C*), encroaching slightly on the lateral nuclei of the thalamus.

4. Sections at the level of the merging of the third ventricle with the aqueduct of Sylvius displayed symmetric lesions in the region of the nuclei of the posterior longitudinal bundle (fig. 6*D*).

COMMENT

Earlier investigators, beginning with Mauthner, assumed that the state of sleep is the result of an interruption in the upward stream of

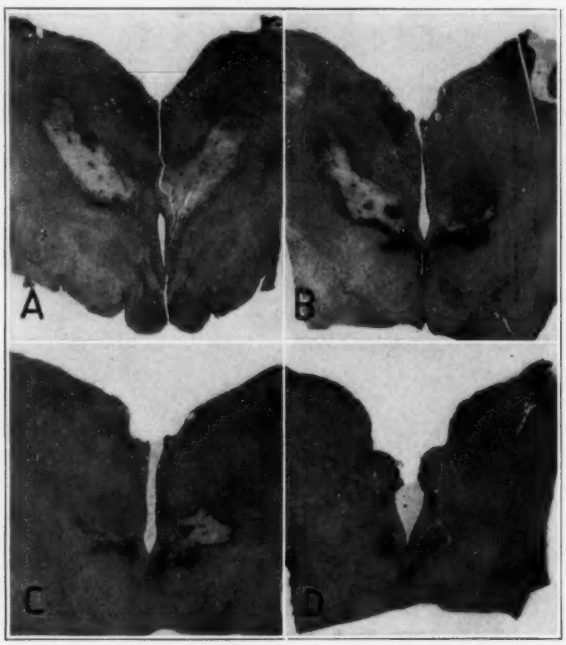

Fig. 6 (case 2).—*A*, section at the level of the massa intermedia and mamillary bodies, showing that the lesions involve partly the massa intermedia, the periventricular gray matter of the hypothalamus and the lateral nuclei of the thalamus. *B*, section at the level of the posterior end of the third ventricle, showing that the lesions are bilateral and extend from the midline in the region of the subthalamus, just above the red nuclei. *C*, section at a level somewhat caudad to that in *B*, showing lesions close to the midline which spread out laterally in the subthalamic region. *D*, section at the point of mergence of the third ventricle with the aqueduct of Sylvius, displaying a symmetric lesion in the region of the nucleus of the posterior longitudinal bundle.

sensory impulses, which deprives the cerebral cortex of their stimulating influence. They further assumed that this interruption occurred primarily in the region of the rostral end of the mesencephalon and the

adjacent part of the diencephalon. A recurrent swelling of tissue in these areas of the brain stem was thought by Mauthner to block the passage of the impulses which are essential to maintain wakefulness. Troemner advanced a somewhat similar theory, based on the assumption that lack of stimulation is the probable cause of sleep.

Objections were raised against such theories, as it was pointed out that pathologic somnolence may occur with intact sensory streams and that normal rhythm between sleep and wakefulness can exist in animals without a cerebral cortex, the recipient of the sensory impulses. These objections, however, are met by Ranson's concept of a block, which in his belief interrupts the downward drive of impulses, resulting in sleep.

In passing, it may be mentioned that the conclusions of Piéron,[12] which point to the presence of fatigue products (hypnotoxins) in the circulating blood, capable of inducing sleep, and the hormonic theory of Mingazzini and Barbàra[13] are important concepts which are not in conflict with the idea of the existence of a fairly well localized center in the brain regulating and coordinating all the physiologic phenomena which in aggregate constitute sleep.

Highly significant is the observation by von Economo that in acute lethargic encephalitis disturbances of sleep may take various forms, which include not only somnolence but also inversion and dissociation of sleep, as well as complete asomnia. This, in his opinion, indicates that the postulated center may be affected directly and in many ways: It may be stimulated, depressed or completely inhibited.

Not without importance is the fact that experimental and clinicopathologic evidence places this center in the proximity of nuclear groups which are concerned with the regulation of other important vegetative functions, on the one hand, and the intrinsic, and in part the extrinsic, mechanisms of the eyes, on the other. The significance of this fact is to be found in the observation that changes in metabolism, respiration, pulse rate and position of the eyes and eyelids are known to be part of the general phenomenon recognized as sleep.

Thus it may be assumed that a localized mechanism which regulates sleep exists and that its location can be mapped out on the basis of the known distribution of anatomic lesions in cases of lethargic encephalitis and other disease processes affecting the hypothalamic region of the brain stem. Von Economo placed the center in the wide zone of the

12. Piéron, H.: Le problème physiologique du sommeil, Paris, Masson & Cie, 1913.

13. Barbàra, M.: Il problema della genesi del sonno (le azioni ormoniche regolatrici del fenomeno), Atti d. r. Accad. d. sc. med. in Palermo (1920), 1921, p. 83.

gray matter covering the lateral and posterior walls of the third ventricle and extending into the hypothalamus and mesencephalon (fig. 7), the various cellular groups acting in a mutually balancing mechanism.

In an analysis of the 2 cases here reported clinically and anatomically, it is noted that protracted somnolence was a striking clinical symptom and that at necropsy discretely circumscribed lesions in the diencephalo-mesencephalic region were observed. The lesions were bilateral and symmetric. In part they corresponded closely in location to the lesions produced by Ranson and his co-workers in monkeys with experimentally induced protracted somnolence. The lesions in the human material, however, were somewhat more extensive than those in the experimental

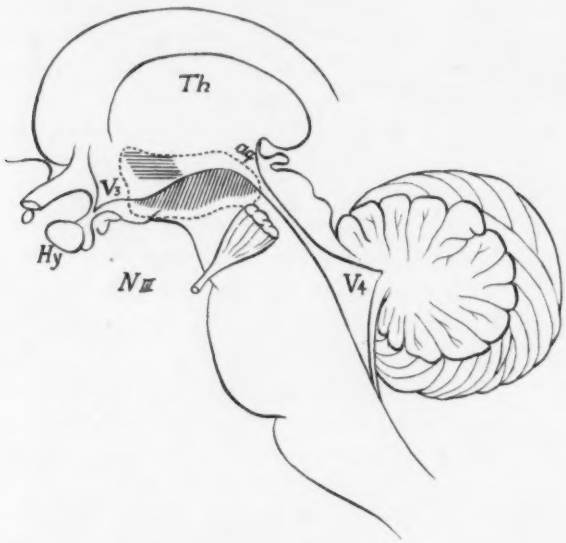

Fig. 7.—Schematic drawing of a sagittal section of the brain stem, showing (shaded area) the location of the sleep-regulating center as outlined by von Economo. *Th* indicates the thalamus; *aq*, the aqueduct of Sylvius; *O*, the optic nerve; *Hy*, the hypophysis; V_3, the third ventricle; *N III*, the oculomotor nerve, and V_4, the fourth ventricle.

animals of Ranson, as they could be traced caudad a short distance beyond the junction of the hypothalamus and the mesencephalon. If it is recalled that the regions thus involved receive their blood supply from a common source [14] and that in both instances described here the lesions were due to disturbances in circulation, then the extent and distribution of these lesions are readily explained.

14. Foix, C., and Hillemand, P.: Les artères de l'axe encéphalique jusqu'au diencéphale inclusivement, Rev. neurol. **32**:705, 1925.

Of significance is the fact that the lesions were bilateral, a condition which, as pointed out by previous observers, is apparently essential for the production of the state of protracted somnolence. The lack of bilaterality is believed to be the explanation for the absence of this manifestation in some cases of tumor in the neighborhood of the third ventricle.

The clinical and the anatomic observations in the 2 cases that have been described support the view that there is a definite region in the hypothalamus the intactness of which is essential in maintaining the more or less rhythmic alternation between the sleeping and the waking state. There is almost full accord between the location of the lesions in the cases described and that of the lesions induced in the experimental animals of Ranson. There is still greater accord between the location of the lesions in the 2 cases here reported and that outlined by von Economo as the center for regulation of sleep.

While the importance of the more caudal parts of the diseased areas, as found in the 2 cases, is still subject to discussion, it seems probable that the periventricular hypothalamic gray matter or the so-called lateral hypothalamic areas, as described by Ranson, are the areas containing cell aggregations which function as a sleep-regulating center.

DISCUSSION AT MEETING OF NEW YORK ACADEMY OF MEDICINE AND NEW YORK NEUROLOGICAL SOCIETY

DR. H. A. RILEY: I wish to ask Dr. Globus whether he has made, or intends to make, any sections of the entire region stained for myelin. In the first case the lesion was in the periventricular nuclei, whereas in the second case the lesion seemed to me to be more in the ventral nucleus of the thalamus, being separated somewhat from the midline by what appeared to be normal tissue. One does not frequently see such exquisitely placed bilateral lesions as these, and I believe, in view of the clinical importance of the cases and the possible correlation with a sleep-regulating center, that it is important for Dr. Globus to locate these lesions as exactly as possible. I believe that the myelin tissue stain would give the best topographic picture.

DR. JOSEPH H. GLOBUS: I have preparations stained for myelin as well as sections stained by the Nissl method. They show that the lesion affects the periventricular gray matter, although it extends beyond that zone into the interior of the thalamus. In this connection, it may be recalled that Cheray, Foix and Nicolesco pointed out that a lesion such as is seen in these cases corresponds to the vascular distribution of a specific blood vessel—a branch of the posterior cerebral artery which supplies the posterior end of the thalamus as well as the anterior quadrigeminal body. It is for this reason that such a lesion frequently causes disturbances in the extrinsic and intrinsic muscles of the eyes, in addition to somnolence.

ABSTRACT OF DISCUSSION AT ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

Dr. Percival Bailey, Chicago: I had the privilege of reading Dr. Globus' paper before this meeting, and now I have seen the location of the lesions on the lantern slides. I should like to raise two questions: The first concerns the value of pathologic lesions in the localization of function in a portion of the brain, and the second concerns the differential diagnosis of sleep and coma. Concerning the first question, I might point out that the lesions in Dr. Globus' paper were probably much wider than necessary to produce this syndrome of pathologic sleep. Dr. Globus has also indicated that in his paper. He did not have time to insist on it in the presentation of the lantern slides.

Dr. Fulton and I once described a case in which the sleep syndrome was much more typical than that in these cases and in which the lesion was confined exclusively to the hypothalamus, without impinging in any way on the thalamus or on the midbrain. It is probable that the extension of the lesion in the present cases was the cause of a certain comatose aspect of the clinical syndrome which differentiates it somewhat from pure sleep.

That brings me to the second point, namely, the differential diagnosis of sleep and coma. I did not have the opportunity of observing these patients, and therefore it is impossible for me to determine how nearly the syndrome which they presented resembles sleep. Evidently Dr. Globus had some question about that in his own mind, for he states that in the first case the patient had stertorous breathing and Cheyne-Stokes respiration. In the second case he states that the patient remained comatose. It is obvious that the condition the patient presented was not physiologic sleep, and Dr. Globus did not maintain that it was such.

Perhaps in the present instance the distinction is not of any great importance, for I am persuaded that the lesion of the brain which disturbs consciousness is very near the lesion which disturbs sleep. Both syndromes depend largely on the total influx of sensory stimuli to the central nervous system, and much of that sensory influx is to this particular region—the midbrain, the hypothalamus and the periaqueductal region—so that a lesion in this neighborhood will disturb not only sleep but also consciousness to a certain extent; it is, therefore, not unusual or unexpected that the two should be closely allied and that one should find in such cases not pure sleep but a certain amount of stupor or coma, or whatever one wishes to call it, in addition to pathologic sleep.

Dr. John F. Fulton, New Haven, Conn.: I shall restrict my comments to several physiologic aspects of the subject. Sleep is governed by essentially autonomic mechanisms. Activity of the sympathetic division of the autonomic system promotes wakefulness, and it leads to exhaustion of the bodily resources, as Cannon's work has so clearly indicated. If opposing parasympathetic "centers" are destroyed the sympathetic system then becomes ascendant and discharge occurs along its several divisions. The animal (or the patient) is alert and awake and ready for flight or fight. This, I say, is the opposite of sleep. From the point of view of neurologic mechanisms and central representation, it is now known, through the work of Bard, Ranson and others, that the primary focus of the sympathetic mechanism lies in the posterior portion of the hypothalamus. The regions which were destroyed in the 2 cases just described included these sympathetic areas.

I would, therefore, venture to differ in a somewhat academic way with Dr. Globus in the interpretation of these results. Sleep, it seems to me, is essentially

not a sympathetic, but a parasympathetic, mechanism. In those circumstances in which the parasympathetic division of the autonomic system is released and allowed to execute its activities unimpeded one witnesses certain phenomena: The heart rate becomes slow; the basal metabolic rate is lower; the pupils become constricted; peristalsis goes on merrily; the bodily reserves are restored, and the body as a whole becomes prepared again for active existence. These mechanisms are regulated, in part at least, by the anterior portion of the hypothalamus. In those circumstances in which the anterior hypothalamus and its mechanisms are in the ascendant, and in which the posterior hypothalamus is suppressed (through activity of the anterior hypothalamus, or through activity of the cortex), one witnesses the phenomena of sleep.

I agree with Dr. Globus that destruction of the sympathetic centers, which leaves the parasympathetic division in the ascendant, leads to the appearance of sleep, but the phenomenon is one affecting the whole nervous system, including the cerebral cortex; the cerebrum is in immediate relation with the hypothalamus; e. g., the mamillary bodies, through the tract of Vicq d'Azyr, send an enormous connection to the anterior thalamus and thence to the cingulate gyrus; there are at least half a dozen other pathways by which the cerebral cortex is connected with the hypothalamus, directly or mediately through a chain of nuclei. With that thought in mind, one may mention the concept of Pavlov that suppression of cortical activity is an essential concomitant of sleep; this is certainly essential to any theory of sleep. Just how that suppression occurs is still a matter of conjecture, but no doubt the region of the hypothalamus is the most important in the regulation of the sleep process, and when the sympathetic division is thrown out of action, as in the cases which Dr. Globus describes, the cerebral cortex becomes in some manner inhibited.

Dr. Joseph H. Globus, New York: Dr. Bailey has called my attention to the fact that I made no mention of the condition of the brain outside the areas in which I described definite pathologic alterations. Now, the cerebral cortex and the subcortex, as well as other parts of the brain outside the areas in which definite lesions were found, showed no alteration which could be associated with the physiologic changes manifested by the patient. In presenting my paper, I assumed that interest was primarily in the positive observations.

Dr. Bailey mentioned also that in the instances that he and Dr. Fulton described in which tumors of the brain produced protracted somnolence they observed no lesions as vast as those noted in my cases. The absence of obvious lesions in their cases does not exclude the possibility that physiologic alterations may have occurred in the regions proximal to the tumor in question. Since the tumors described by Dr. Bailey and Dr. Fulton were in the neighborhood of the hypothalamic region, there is a strong probability that parts of the brain adjacent to the tumor showed physiologic alterations, although obvious anatomic changes were not apparent to the eye.

As to whether the condition was protracted somnolence or coma: I may say that the first patient, whom I observed throughout her entire residence in the hospital, was not in coma but was unquestionably in a state of protracted somnolence closely simulating ordinary sleep. She could be awakened and could be fed during these short moments of wakefulness. She was asked questions to which she gave intelligent answers. In the second case, the patient came under my observation toward the end of the clinical course; for that reason I had to accept the interns' first description of the state of somnolence as a comatose condition, but when

she came under my direct observation, again I found that this was not a case of coma but one of somnolence, although it was deeper than that noted in the first instance.

I agree with Dr. Bailey that whether the condition is to be labeled somnolence or a comatose state is not important, since in either event the lesion in the hypothalamic region is probably responsible for the suspended wakefulness characterizing both states.

I am also in full agreement with the views expressed by Dr. Fulton with regard to the possibility that the corticohypothalamic drive is interrupted in the area affected by disease, and that in this way suspension of activity, which is called sleep, is protracted.

Case Reports

VENTRICULOGRAPHIC DIAGNOSIS OF AGENESIS OF THE CORPUS CALLOSUM

ADAM KUNICKI, M.D., AND JERZY CHOROBSKI, M.D., WARSAW, POLAND

Total or partial absence of the corpus callosum, a developmental anomaly of rare occurrence,[1] was until lately diagnosed only at autopsy. Its recognition during life was made possible by the development of pneumoencephalography. Five cases in which diagnosis was made by this method were presented by Hyndman and Penfield [2] at a meeting of the American Neurological Association in June 1934. Independently, Davidoff and Dyke [3] reported at the same meeting 3 similar cases.

Operative inspection of the lesion in the second case of Hyndman and Penfield [2] and autopsy in the second case of Davidoff and Dyke [3] gave a clue to the understanding of the pneumoencephalographic picture of agenesis of the corpus callosum. Hyndman and Penfield concluded that the following features are of primary importance in the diagnosis of this condition: (1) "symmetrical separation of the anterior horns, with a moniliform shadow of gas between them which is continuous with the third ventricle below and rises higher than this ventricle should"; (2) "an almost right-angled shelving or bicornuate appearance of the bodies of the lateral ventricles." The latter, in their opinion, is pathognomonic.

Those who saw this unusual picture for the first time thought they were dealing with a cyst of the cavum septi pellucidi. This misinterpretation of the pneumoencephalograms is, of course, explicable by the rarity of agenesis of the corpus callosum. Actually, however, in cases of this anomaly, an accurate analysis of the shape of the mesial wall of the lateral ventricle and of the position and size of the central, domelike shadow of air permits no diagnosis other than that of absence of the corpus callosum. The pneumoencephalographic picture obtained in these cases differs entirely from that seen in cases of an enlarged cavum septi pellucidi.

From the Neurosurgical Division of the Neurological Clinic, J. Pilsudski University.

1. Of the 100 or more cases of agenesis of the corpus callosum reported, the condition in 90 was associated with other congenital defects, either mental or physical (de Morsier, G., and Mozer, J. J.: Agénésie complète de la commissure calleuse et troubles du développement de l'hémisphère gauche avec hemiparésie droite et intégrité mentale [Le syndrome embryonnaire précoce de l'artère cérébrale antérieure], Schweiz. Arch. f. Neurol. u. Psychiat. **35**:64, 1935).

2. Hyndman, O. R., and Penfield, W.: Agenesis of the Corpus Callosum: Its Recognition by Ventriculography, Arch. Neurol. & Psychiat. **37**:1251 (June) 1937.

3. Davidoff, L., and Dyke, G.: Agenesis of the Corpus Callosum: Its Diagnosis by Encephalography, Am. J. Roentgenol. **32**:1, 1934.

So long as an enlarged cavum septi pellucidi does not communicate with the ventricular system it cannot be filled with air introduced into the ventricles. Such a cavum, containing more or less fluid, acts as a space-occupying lesion. In spite of this, the separation of the anterior horns and the bodies of the lateral ventricles seems only spurious, the mesial walls of the lateral ventricles being only invaginated by the centrally situated mass. Should the anterior portions of the lateral ventricles be actually separated and their mesial walls show a filling defect, there would never be, with a cyst of the cavum septi pellucidi, a central shadow of air rising higher than the third ventricle, because the cyst, located above that ventricle, would prevent its upward elongation.

With a communicating cyst of the cavum septi pellucidi the air introduced into the ventricular system will, of course, enter the enlarged cavum; its more or less moniliform shadow may or may not be continuous with the shadow of the third ventricle below, and it will rise higher than this ventricle. There will be no separation of the anterior portions of the lateral ventricles or filling defect in their mesial walls, the ventricular air passing freely, through the perforated septum pellucidum, from one ventricle to the other. Should the cavum septi pellucidi communicate with only one lateral ventricle, the other wall being unperforated, the shadows of air in the lateral ventricles will approach each other in the midline, the separating unperforated wall of the cavum either being vertical or deviating from the ventricle containing air under a higher pressure toward the ventricle in which the pressure of air is lower. At all events, there will be no separation of the lateral ventricles.

In short, a noncommunicating cyst of the cavum septi pellucidi may invaginate the mesial walls of the lateral ventricles, or may even separate the ventricles, but the only centrally located shadow of air will eventually be that of the third ventricle. The last may be of normal size and shape, or even be compressed from above. In the case of a communicating enlarged cavum septi pellucidi the ventriculogram may show a more or less moniliform central shadow of air communicating with the lateral ventricles and—but not necessarily—with the third ventricle below, and rising higher than this ventricle. There will be neither separation of the anterior portions of the lateral ventricles nor a filling defect in their mesial walls.

Difficulties may be encountered in the differential diagnosis of complete and partial agenesis of the corpus callosum. A diagnosis of the latter was made in 2 of the 5 cases of Hyndman and Penfield.[2] In the first case the condition was recognized as partial agenesis only as a result of operative inspection of the lesion, the pneumoencephalogram being almost entirely identical with that of complete agenesis. Without the operative observations it would hardly have been possible to make a diagnosis of partial absence of the corpus callosum. It is probable that the existing portion of the corpus callosum was thin and not very resistant and that there was also absence of the septum pellucidum. In the second case the ventricular system, as seen in the anteroposterior view, seemed to be almost normal, whereas in a lateral roentgenogram an abnormal notch in the intrathalamic portion of the third ventricle, directed upward and posteriorly, indicated absence of the resistant

barrier of the corpus callosum. In a third case the persistence of remnants of the corpus callosum was not entirely obvious.

A case of total agenesis of the corpus callosum, observed personally, is the ninth in which this condition has been recognized during life, and the second in which the diagnosis has been confirmed by both operative inspection and autopsy.

REPORT OF A CASE

Clinical History.—R. M., a boy aged 21 months, was referred on Sept. 21, 1938 by Dr. M. Bussel, of the pediatric clinic of the J. Pilsudski University. The third child of healthy parents, he was born at full term. Until 1 year of age he seemed well, although the parents admitted that he had never raised his head or tried to talk or to sit up. One could not secure contact with him; he recognized no one, not even his parents, and no articulate sounds were elicited

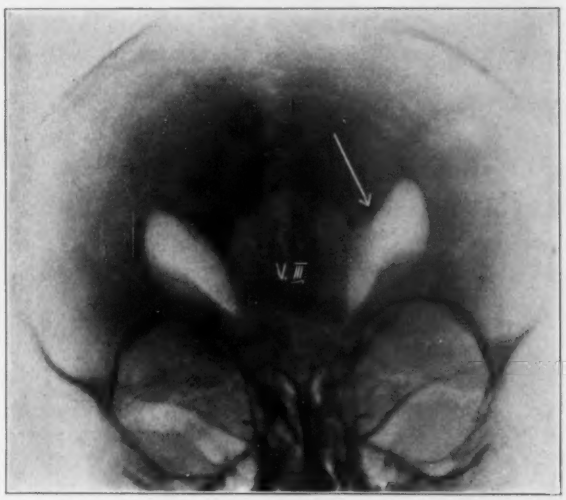

Fig. 1.—Encephalogram showing complete agenesis of the corpus callosum. *V. III* indicates the third ventricle.

from him. He slept most of the time, but when awake continually sucked a pacifier. The child never changed his position spontaneously, and when placed in a sitting posture fell backward without the slightest attempt to maintain his equilibrium.

Examination.—Height and weight were normal for a child of his age. The skin was dry. The internal organs were normal, but there was cryptorchidism on the right. No signs of meningeal irritation were found. The skull was large and high, and its anteroposterior diameter was somewhat shorter than normal. Although there was no cracked pot sound on percussion, there was a peculiar percussion note, such as is sometimes obtained in hydrocephalic skulls. Both optic nerves were atrophic; there were nystagmoid movements on gazing to either side. Muscle tonus was variable in all extremities, and all movements were clumsy, aimless and ataxic. The tricipital and bicipital reflexes were weak on both sides; other reflexes were brisk, but equal. The Babinski, Rossolimo and Mendel-Bechterew signs were present bilaterally.

Encephalographic Studies.—Pneumoencephalograms were made at the pediatric clinic after the spinal injection of air. Only the anteroposterior roentgenogram (with the occiput presented) was sufficiently good for accurate analysis. The lateral ventricles were separated (fig. 1), and between them was a fainter, but clearly visible, shadow of air rising in a domelike manner almost to the upper level of the lateral ventricles. The shape of the lateral ventricles was also abnormal. They were elongated, and their upper poles inclined outward. The upper wall ran

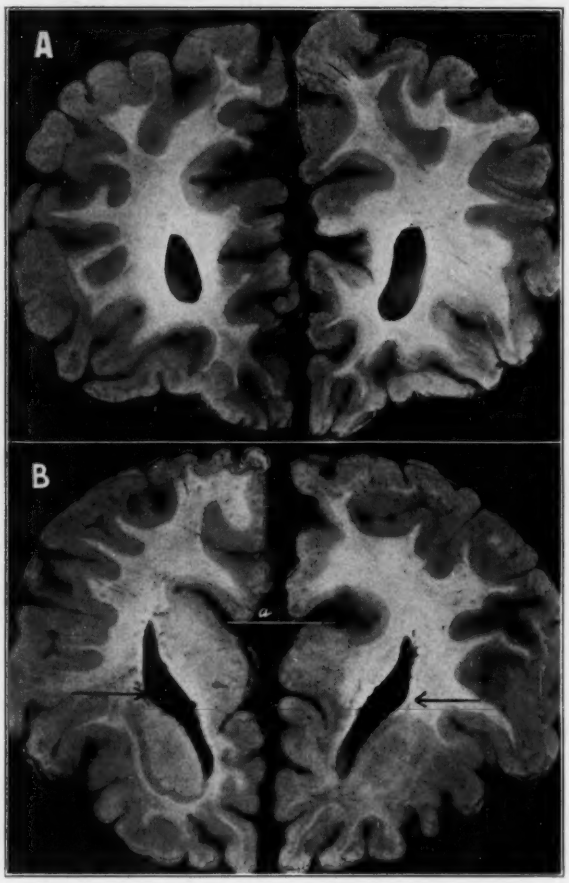

Fig. 2.—*A*, cross section of the brain 2.5 cm. anterior to the optic chiasm. *B*, cross section of the brain 1 cm. posterior to that shown in *A*. The horizontal furrow (*a*) corresponds to the level of the corpus callosum.

from a lateral position above mesially and downward to a point marked by the arrow (fig. 1), where it made an angle and passed gradually into the domelike portion of the central shadow of air. The angle between the upper wall of the lateral ventricle and the upper wall of the central shadow of air was more acute on the right side than on the left. The mesial wall of the left lateral ventricle was more vertical than that of the right.

Course.—Because of the atrophy of both optic nerves, it was thought advisable, in spite of the preoperative diagnosis of complete absence of the corpus callosum, to explore the chiasmal region in order to exclude the possibility of a lesion compressing the optic nerves, independent of the agenesis of the corpus callosum. Accordingly, on September 26 a right frontal osteoplastic craniotomy was performed, and after negative exploration of the chiasmal region the right frontal

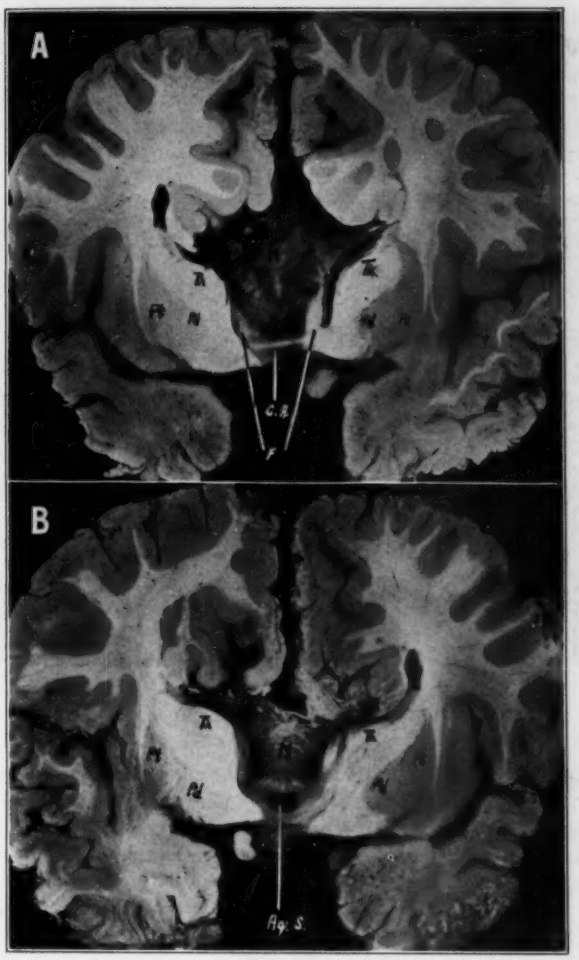

Fig. 3.—*A*, cross section of the brain just behind the anterior commissure. Here and in *B*, *M* indicates the meningeal membrane; *Th*, the optic thalamus; *Pt*, the putamen; *Pd*, the pallidum; *C.A.* the anterior commissure, and *F*, the columna fornicis. *B*, cross section of the brain through the posterior portion of the third ventricle. *Aq.S.* indicates the aqueduct of Sylvius.

lobe was retracted from the falx cerebri. In lieu of the corpus callosum a delicate, transparent membrane, covering a fluid-containing space, was observed. The membrane was punctured and a large amount of cerebrospinal fluid withdrawn. The gyri in the frontal area were malformed, and the overlying pia-arachnoid was

thickened and opaque. The child left the operating room in good condition, but died nine hours later, with signs of acute respiratory failure.

Autopsy.—Postmortem examination, performed the next day, revealed no apparent reason for the sudden death. A detailed description of the microscopic examination of the brain will appear later. Here only its most conspicuous macroscopic anomalies are enumerated. The cerebrum weighed 1,191 Gm. The fissures of Sylvius were almost vertical, and the parietal lobes—in accordance with the shortening of the anteroposterior diameter of the skull—seemed to be shorter than normal, their gyri being very small. Microgyria was seen also in other regions of the brain; the gyri were crowded, and their course was chaotic. The olfactory tracts were normal; the optic nerves were unusually thin and elongated; the floor of the third ventricle was bulging; the corpora mamillaria were absent. The pons was small and thin and the medulla oblongata narrow.

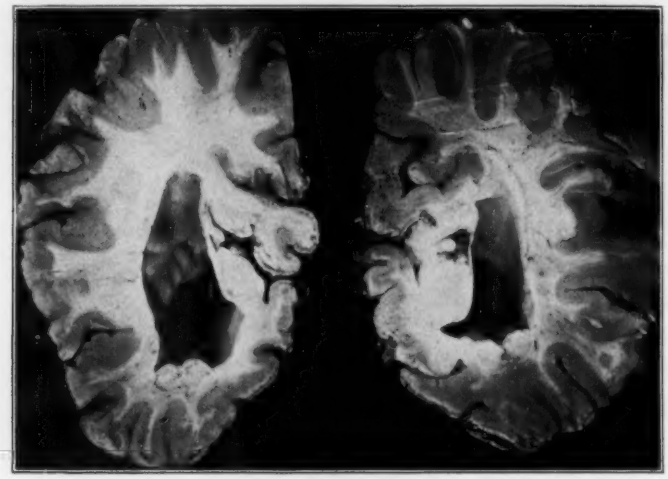

Fig. 4.—Cross section of the brain posterior to the optic thalami. On both sides, but especially on the left, one sees the subependymal tuberosities.

In frontal cross sections of the brain the most important feature was the appearance of the ventricular system. This enabled us to interpret the encephalographic appearance of absence of the corpus callosum, as follows: 1. A cross section 2.5 cm. anterior to the chiasm (fig. 2*A*) passed through normal anterior horns of the lateral ventricles. Absence of the corpus callosum was obvious. 2. A section 1 cm. posterior to the first demonstrated the S-shaped elongation of the ventricles (fig. 2*B*). Their upper poles were inclined outward. The lower bend in the external wall of the ventricles (the portion beneath the arrows) was caused by the head of the caudate nucleus. The mesial horizontal furrow (fig. 2*B*, *a*) corresponded to the level at which the corpus callosum is normally found. 3. The next cross section (fig. 3*A*), just behind the anterior commissure, showed the columnae fornicis leaving the commissura anterior and arching upward and laterally. The space between them, covered by a thickened pia-arachnoid, was occupied by the convolutions of the brain. This meningeal membrane passed posteriorly and formed the roof of the third ventricle, communicating with the space limited by the columnae fornicis. The mesial convolutions of each hemi-

sphere were invaginated into the lumen of the lateral ventricle, which was thus narrowed. Figure 3*B* shows the third ventricle definitely dilated, the distance between the optic thalami, which were very small, being about 2 cm. There was complete absence of the gray commissure. In the depth of the third ventricle one saw the commissura posterior and the entrance to the dilated aqueduct of Sylvius. The undeveloped choroid plexus of the third ventricle was attached to the lateral edge of its meningeal roof. Above the optic thalami were the lateral ventricles, seen in cross section. Their shape resembled that of the horns of a buffalo. 4. The cross section posterior to the optic thalami demonstrated the dilated posterior portions of the lateral ventricles, their walls showing subependymal tuberosities (fig. 4), which on microscopic examination were seen to be ectopias of the cerebral cortex.

The gross anatomic malformations of the brain were: agenesis of both the corpus callosum and the septum pellucidum; partial defect in the body of the fornix; complete absence of the commissura fornicis and of the mamillary bodies; microgyria; maldevelopment of the optic thalami, and complete absence of the commissura grisea.

SUMMARY

The anomalies of the ventricular system, as seen in the pneumoencephalogram of this patient, were caused by agenesis of the corpus callosum and septum pellucidum. The encephalogram had all the characteristics observed in the similar cases of Hyndman and Penfield [2] and Davidoff and Dyke.[3] First, there was separation of the anterior portions of the lateral ventricles without the presence of a filling defect in their mesial walls. Second, the roof of the lateral ventricles did not run horizontally, as it normally does, but descended from a lateral position above downward and mesially. In its course it made an obtuse angle, produced by the optic thalamus (hence "the bicornuate appearance of the bodies of the lateral ventricles" of Hyndman and Penfield). Third, the central space limited by the lateral ventricles was occupied by a shadow of air, the upper outline of which was domelike. It rose higher than the level of normal attachment of the tela choroidea of the third ventricle. This shadow represented the third ventricle enlarged as the result of the absence of the corpus callosum. Fourth, the floor of the third ventricle was on a level with the lower poles of the lateral ventricles, instead of being somewhat below them.

Abstracts from Current Literature

Physiology and Biochemistry

Effect of Iodoacetic Acid on the Carbohydrate Metabolism of Isolated Mammalian Tissues. S. B. Barker, Ephraim Shorr and M. Malam, J. Biol. Chem. **129**:33, 1939.

Barker, Shorr and Malam have shown that measurements of respiratory exchange indicate that mammalian brain and smooth, skeletal and cardiac muscle can oxidize carbohydrate as readily in the presence of iodoacetic acid sufficient to inhibit 90 to 100 per cent of anaerobic glycolysis (splitting of carbohydrate to lactic acid) as in its absence. Added dextrose is as effectively oxidized under these conditions as preformed carbohydrate. To insure the validity of the observations it was ascertained that the results obtained were not due to: (1) oxidation of preformed lactic acid, (2) poor aerobic penetration of the iodoacetic acid or (3) production of ammonia from protein. Further corroboration was furnished by the finding that the amount of dextrose disappearing from the solution was quantitatively the same as that calculated from the respiratory data. A striking demonstration of the independence of anaerobic activity and respiration in the case of brain cortex was obtained by a procedure involving merely prolonged washing in Ringer's solution, without the use of any poisons. The addition of small amounts of dextrose showed that qualitative as well as quantitative separation could be obtained, oxygen consumption leveling off at a dextrose concentration of about 20 mg. per cubic centimeters, while anaerobic glycolysis was still increasing at a concentration of 200 mg. per hundred cubic centimeters. This evidence is considered against any theory of carbohydrate oxidation which assumes formation of lactic acid as a necessary intermediary. It supports the concept of functional independence of aerobic and anaerobic mechanisms. In the case of the testis, anaerobic glycolysis could not be inhibited without a corresponding depression in respiration.

Page, Indianapolis.

Effect of Deficiencies in Riboflavin and Other Heat-Stable Vitamin B Components. A. Baird Hastings, J. Muus and O. A. Bessey, J. Biol. Chem. **129**:295, 1939.

It has become increasingly apparent that the members of the group of compounds belonging to the vitamin B complex are concerned with the oxidations carried out in certain tissues. The importance of one of these vitamin B factors, riboflavin, for cellular respiration has been established. The present paper by Hastings, Muus and Bessey is concerned with the metabolism of liver and muscle of rats which had been maintained on a diet (*a*) deficient in riboflavin, (*b*) deficient in components of the heat-stable vitamin B complex other than riboflavin or (*c*) deficient in both riboflavin and the yeast extract. Diets deficient in the heat-stable components of the vitamin B complex present in yeast were found to produce a decrease of 22 per cent in the oxygen consumption of rat liver and an increase of approximately 30 per cent in the oxygen consumption of rat diaphragm. The two effects are to be attributed to difference in the chemical substances. Only the increase in diaphragm metabolism occurs when the diet is deficient in riboflavin. Addition of crystalline riboflavin to the diet causes the diaphragm metabolism to return to normal values. Only the decrease in liver metabolism occurs when the yeast extract is omitted from the diet but riboflavin is included. The decrease in liver metabolism is associated with fatty infiltration and probably does not represent a specific alteration in the metabolic process of the active liver cells.

Page, Indianapolis.

THE LECITHIN, CEPHALIN AND SPHINGOMYELIN CONTENT OF NORMAL HUMAN ORGANS. S. J. THANNHAUSER, J. BENOTTI, A. WALCOTT and H. REINSTEIN, J. Biol. Chem. **129**:717, 1939.

Thannhauser and his co-workers find that human brain contains five to six times as much sphingomyelin as any other organ. Cephalin is present in much greater amounts than in other organs, and lecithin, in about the same amount.

PAGE, Indianapolis.

THE DISTRIBUTION OF CREATINE AND CREATININE IN THE TISSUES OF THE RAT, DOG AND MONKEY. ZELMA BAKER and B. F. MILLER, J. Biol. Chem. **130**: 393, 1939.

Concentrations of creatine and creatinine in the tissues of the rat, dog and monkey have been determined by specific enzyme methods. In muscle and testis the values agree fairly closely with the "apparent" concentrations found by non-specific technic. However, in many other tissues, notably liver, it has been demonstrated that the concentrations of true creatine and creatinine are much lower than those hitherto accepted. Also, a fairly constant ratio has been found between the concentrations of true creatine and creatinine in various tissues. Rat brain contains 156 mg. of apparent creatine in 100 Gm. of tissue, of which 26 mg. is residual chromogen and 130 mg. true creatine, the values being comparable with those for muscle and testis and in contrast with those for lung, liver and spleen.

PAGE, Indianapolis.

BIOCHEMICAL CHANGES OCCURRING IN THE CEREBRAL BLOOD DURING THE INSULIN TREATMENT OF SCHIZOPHRENIA. HAROLD E. HIMWICH, KARL M. BOWMAN, JOSEPH WORTIS and JOSEPH F. FAZEKAS, J. Nerv. & Ment. Dis. **89**:273 (March) 1939.

By studies on simultaneously drawn specimens of arterial and jugular blood, Himwich and his associates investigated the biochemical changes induced by the insulin treatment of schizophrenia. The changes observed in the metabolism of the brain during hypoglycemia are not characteristic of schizophrenia, since they are present in patients with psychoneurosis, in normal persons and also in lower animals. Himwich and his associates found that before insulin was injected the average utilization of oxygen by the brain was 7.04 volumes per cent and that of dextrose 12.5 mg. per hundred cubic centimeters. After injection of insulin, when patients were in a precomatose condition the sugar content of arterial blood was between 13 and 37 mg. per hundred cubic centimeters, the average absorption of oxygen was 6.19 volumes per cent and that of dextrose 7 mg. per hundred cubic centimeters. During coma the sugar content of arterial blood was between 8 and 33 mg. per hundred cubic centimeters, utilization of oxygen was reduced to 3.07 volumes per cent and that of dextrose to 4.16 mg. per hundred cubic centimeters. It was also observed that there was no constant absorption or utilization of lactic acid by the brain during hypoglycemia and no change in esterase activity. The neurologic signs occurring during hypoglycemia were: first, motor restlessness then clonic twitches, primitive movements, pathologic reflexes and extensor spasms, and, finally, loss of muscle tone, disappearance of pathologic reflexes and defense reactions, and complete areflexia. These signs may be divided into evidences of cerebral stimulation, due to mild reduction of oxidation, and those of cerebral depression, due to severe reduction of oxidation. Higher cortical centers are affected earliest by this sequence of stimulation and depression, while lower centers in the hypothalamus and other subcortical regions are involved only later. These neurologic changes, like the alterations in mental functions, seem to depend on changes in cerebral metabolism, but the mechanism whereby normal processes are substituted for abnormal is unknown.

MACKAY, Chicago.

AUTONOMIC FUNCTIONS OF THE CEREBRAL CORTEX. RICHARD L. CROUCH and J. KENNETH THOMPSON, J. Nerv. & Ment. Dis. **89**:328 (March) 1939.

Crouch and Thompson report the effects on autonomic functions of electric stimulation of the cerebral cortex in cats, dogs and macaque monkeys. Their observations were restricted to pupillary reactions and changes in the blood pressure and pulse rate, with a few notes on other autonomic reactions. In all animals it was discovered that the region from which responses were most easily obtained was at the junction of the motor and the premotor area, but more definitely in the latter. In the cat and dog this was at and about the junction of the frontal and anterior sigmoid gyri, while in the monkey it was in the superior frontal gyrus and the adjoining portions of the precentral gyrus. The results of stimulation varied somewhat with the degree of anesthesia and with other physiologic variables, but included, in general, dilatation of the pupils in all animals, elevation of blood pressure in the cat and monkey and a fall of blood pressure in the dog. The pulse rate was increased usually in the cat and monkey, and inconstantly in the dog. Copious salivation, defecation and micturition were also noticed in most animals. Crouch and Thompson point out that the various autonomic functions were more or less equally affected by stimulation of given cortical areas, and that there seemed to be no differential cortical representation for different autonomic functions. The type of reaction was predominantly sympathetic in the cat and monkey and parasympathetic in the dog, without separate areas for sympathetic and parasympathetic reactions. Variations in the responses were apparently based on changes in the physiologic state of the animal and of the cortex.

MACKAY, Chicago.

MECHANISM OF CARDIAZOL [METRAZOL] CONVULSIONS. D. J. WATTERSON and R. MACDONALD, J. Ment. Sc. **85**:392 (May) 1939.

Watterson and Macdonald performed experiments to determine whether metrazol, after intravenous injection, has time to reach the central nervous system before the convulsion occurs. They found that after 0.5 cc. of a 2 per cent solution of sodium cyanide is injected intravenously reflex hyperpnea occurs when the drug reaches the carotid sinus. The hyperpnea is characteristic, consisting of two or three sudden deep inspirations; it is best seen if the subject relaxes in a semirecumbent position. In these experiments 12 cooperative patients were given intravenously convulsion-producing doses of metrazol mixed with 0.5 cc. of a 2 per cent solution of sodium cyanide. In each case the characteristic hyperpnea due to stimulation of the carotid sinus occurred a second or two before the convulsion began. The experiments show that the metrazol passes the carotid sinus before the convulsion begins and that the convulsion is clearly demarcated from the reflex hyperpnea. In fact, the short interval following the hyperpnea is probably long enough to allow the metrazol to reach all parts of the brain. Experiments are described which show that under appropriate conditions carbaminoylcholine, acetylbetamethylcholine and sodium cyanide inhibit the metrazol convulsion. Caffeine, administered either orally or intravenously, does not inhibit the convulsion. The conclusion is drawn that cerebral vasodilatation inhibits the convulsive action of minimal convulsion-producing doses of metrazol. It is suggested that the increased rate of cerebral blood flow rather than cerebral vasodilatation itself is the important factor in the inhibition.

J. A. M. A.

SENSORY ADAPTATION AND THE MECHANISM OF VISION. K. J. W. CRAIK, J. Physiol. **96**:1P, 1939.

Craik investigated the effect on the subjective sensation of brightness of adaptation of the eye to various degrees of illumination. Increase in illumination increased the sensation of brightness, even in the adapted eye, to about 100 equivalent foot candles. Beyond that degree of illumination, no further increase in the sensation of brightness was produced, but the unadapted eye could detect changes in illumination throughout the entire range.

THOMAS, Philadelphia.

THE EFFECT OF INSULIN HYPOGLYCAEMIA AND B_1-AVITAMINOSIS ON THE ACETYLCHOLINE CONTENT OF BRAIN. F. C. MACINTOSH, J. Physiol. **96**:6P, 1939.

Insulin hypoglycemia and B_1 avitaminosis were without significant effect on the acetylcholine content of the brains of mice and pigeons.

THOMAS, Philadelphia.

DISCHARGES IN NERVE FIBRES PRODUCED BY POTASSIUM IONS. G. L. BROWN and F. C. MACINTOSH, J. Physiol. **96**:10P, 1939.

Brown and MacIntosh observed that injection of solutions of potassium chloride into the blood vessels supplying nerve trunks caused a discharge of nerve impulses in the fibers of the nerve at a frequency of about 150 per second. They question whether the discharges from sympathetic ganglia that follow injections of potassium chloride are due solely to stimulation of ganglion cells.

THOMAS, Philadelphia.

COMPULSIVE GRASPING, THE GRASP REFLEX, TONIC INNERVATION AND ASSOCIATED PHENOMENA. I. M. ALLEN, M. J. Australia **1**:717 (May 13) 1939.

Allen studied the phenomena of grasping and tonic innervation in 16 cases in which there were cerebral lesions. The observations confirmed the occurrence in the human subject of two groups of phenomena: one labile, fully coordinated and sometimes, but not always, amenable to being brought under voluntary control, and the other a fixed pattern, arising from a constant stimulus and usually, but not always, insusceptible of being brought under voluntary control. The first type occurs in response to visual or tactile stimulation or to both. Visual stimulation consists in movement toward and the grasping of an object presented at a short distance from the hand. Tactile stimulation is more effective than visual stimulation and the two together are more effective than either of them alone. When completed, the grasping is under voluntary control. At the beginning, however, it is compulsive. Sometimes it is controlled voluntarily or at command at the outset; at times it is controlled and then bursts past the control, and at others it appears at once in spite of attempts to control it. It is evidently related to integrations at the cortical level and is at least analogous to the repeated sucking response observed in 1 patient. The second group arises in response to stretch and appears even when visual and tactile stimulation is impossible. It is observed in the muscles of the limbs, in the hand and foot and in the jaw. It consists in increase of muscle tone with, in the hand, a grasp which increases as the stimulation continues and, in the jaw, traplike closure of the mouth and teeth on the stimulating object. It arises primarily and most effectively from stretch of the flexors of the thumb and index finger. It is not prevented by the patient either voluntarily or at command, but in its minor forms the grasp can be stopped and undone at command, even though the appropriate stimulation continues. It is evidently operative at a level below that of the cerebral cortex. It appears that the two groups of phenomena cannot be rigidly separated and that they are mutually dependent and interact in the human subject. The position of the patient in space affects the two groups of phenomena; that is, in the lateral position they are increased in the uppermost limb and decreased in the undermost limb. Both the first and the second group of phenomena appear to interact closely with the righting mechanism or to form an integral part of it. The term "compulsive grasping" appears to be appropriate to the compulsive phenomena forming the first group, "tonic innervation" to those of the second group and "grasp reflex" to those of the second group in the hand.

J. A. M. A.

ELECTROENCEPHALOGRAPHIC STUDIES ON EPILEPSY. O. SAGER and A. KREINDLER, J. belge de neurol. et de psychiat. **39**:265 (April) 1939.

Sager and Kreindler found that the electroencephalogram shows abnormalities of two types during a petit mal attack; one consists of series of waves occurring

in regular succession and averaging 3 per second, the other, of waves of the same frequency interspaced, however, by waves of differing frequency. The electroencephalogram is entirely normal between attacks. In grand mal seizures the electroencephalogram shows modification in the frequency of the waves and in the relationship of waves of different frequency, and these changes are present also during the interval between the attacks. The findings in petit mal seizures resemble those in convulsions in the rabbit precipitated by the use of atropine, and the grouping of waves in petit mal is similar to that in narcosis induced by evipal (a sodium salt of n-methyl = C = C cyclohexamylmethyl barbituric acid). The authors state that their electroencephalographic researches suggest the participation of subcortical centers in epilepsy. DE JONG, Ann Arbor, Mich.

MECHANISM OF TEMPERATURE REGULATION. S. DONTAS, Arch. f. d. ges. Physiol. **241**:612, 1939.

The effects of various measures on the centers for temperature regulation were studied in dogs and rabbits by observing the production of polypnea as an indicator of the excitability. The body (rectal) temperature at which polypnea appears is considered the threshold of the temperature centers; the difference between the original and the threshold temperature is called the "thermic range." Thirst increases the threshold of polypnea and the thermic range, while the intake of water decreases the thermic range. Injection of hypertonic solutions produces either fever or an increased readiness for the production of fever, while hypotonic solutions of sodium chloride have an antagonistic effect. All pyrogenetic substances, such as bacterial toxins, increase the threshold and the thermic range, while antipyretic drugs act in the opposite direction. The author concludes, contrary to the general conception, that fever is a symptom of paralysis of the temperature centers. This conclusion is apparently based on the fact that he used a heat-dissipating mechanism, such as polypnea, instead of a heat-producing mechanism as an indicator of the excitability of the temperature centers.

SPIEGEL, Philadelphia.

Neuropathology

CEREBELLAR ASTROCYTOMA. P. C. BUCY and W. A. GUSTAFSON, Am. J. Cancer **35**:327, 1939.

Cerebellar astrocytomas occur for the most part in children. They are well circumscribed solid or cystic gliomas, which can usually be readily and successfully enucleated. They are composed predominantly of fibrillary and protoplasmic astrocytes in variable proportions, in association with a very small percentage of other adult and embryonic cells of the spongioblastic series. They contain no ganglion cells or nerve fibers other than those engulfed as a result of their invasion of the cerebellum and no neuroblasts. They not infrequently invade the subarachnoid space, and in such areas one may find glial bridges connecting the molecular layer of the cerebellum and the subarachnoid space. Degenerative changes involving the cells of the tumor, their processes and fibrillae and the blood vessels are common and are not infrequently misinterpreted by the unwary. The surrounding cerebellum shows the effects of compression and ischemia. Although it is possible that many cerebellar astrocytomas are congenital, arising from a developmental fault, this hypothesis remains unproved. There is no evidence to support the contention that these are congenital malformations rather than neoplasms. The small intraneoplasic cysts which develop are the result of liquefaction of the tumor tissue, but the extraneoplastic cysts, and perhaps the large intraneoplastic ones as well, appear to be formed by transudation. The original classification of these tumors into fibrillary and protoplasmic astrocytomas is accurate and valuable. More recent efforts at alteration of the classification or of its nomenclature are illogical, of little value and confusing. FROM AUTHORS' SUMMARY. [ARCH. PATH.]

HEMIATROPHY OF THE BRAIN. BERNARD J. ALPERS and RICHARD B. DEAR, J. Nerv. & Ment. Dis. **89**:653 (May) 1939.

Alpers and Dear report a case of hemiatrophy of the brain and review present knowledge of the condition. The patient, a woman, died at the age of 22 years. Her mother's health had been poor during the pregnancy, which was her second, and the patient was born precipitately. She had severe icterus neonatorum, and her vitality was so low that she almost died when 5 days of age. Her mental and motor development was retarded from the first. At the age of 6 months she had enteritis; of 7 months, bronchopneumonia, and of 10 months, severe pertussis. She was fat and clumsy and had difficulty in maintaining her balance. When 3 years of age she had dysentery. When 5½ years old she had severe convulsions, and there developed paralysis of the left side of the face, the right side of the trunk and the right arm and leg. From this she recovered incompletely, but after the age of 13 years became progressively deaf and had more convulsive seizures. She was mentally deficient and untrainable. She died of bilateral lobar pneumonia.

At autopsy the brain was observed to be small and the leptomeninges markedly thickened and adherent to the brain, especially over and between the frontal lobes. Both hemispheres presented generalized microgyria and simplicity of cortical markings. The left cerebral hemisphere was only one-half as large as the right; all parts of the hemisphere participated in the reduction, except the anterior part of the temporal lobe. The right cerebellar hemisphere was much smaller than the left, while the pons and medulla were markedly reduced in size. On section, the cortex of the left cerebral hemisphere was very narrow; the white matter was excavated and greatly reduced in amount, and the basal ganglia were all much smaller than normal. Miroscopically, the leptomeninges were densely fibrotic and contained many macrophages and multinucleated cells. The meningeal vessels were thickened; some were thrombotic. In the left hemisphere the ganglion cells of the cortex had largely disappeared and were replaced by astrocytes. The lamina zonalis was thickened, and the other layers were not distinguishable. The lamina pyramidalis was much affected in parts, but the Betz cells were still present. There was extensive demyelination of both the cortex and the subcortical structures. In the white matter, arcuate fibers and the centrum semiovale were destroyed, but the fronto-occipital tract and other fibers near the ependyma were spared. The internal capsule on the left was much smaller than that on the right, and the corpus callosum was only a thin myelinated line. There was great loss of cells in the caudate nucleus, putamen and pallidum, with severe gliosis. The cells of the zona compacta in the substantia nigra were unpigmented. The nuclei of the cranial nerves were normal, but one side of the medulla was smaller than the other. Nuclei of the right side of the cerebellum were gone except for a few cells. The pyramidal tract from the left hemisphere was small but myelinated.

Alpers and Dear review the literature and discard many cases as not representing true hemiatrophy of the brain. They restrict this term to cases of complete or nearly complete generalized atrophy of one cerebral hemisphere. They divide the condition into "primary" and "secondary" types, the former occurring at or shortly after birth and the latter arising later in life. The pathologic conditions as described in the literature are summarized. Four theories of pathogenesis attribute the condition to: (1) congenital, (2) inflammatory, (3) vascular and (4) neurogliotic processes. Alpers and Dear believe that the "primary" type, of which their case is an example, is the result of hereditary or congenital factors, including maternal toxins passing through the placenta. The "secondary" types, they think, probably result from encephalomyelitis.

MACKAY, Chicago.

CYSTIC HYDROPS OF THE PINEAL GLAND. AMOUR F. LIBER, J. Nerv. & Ment. Dis. **89**:782 (June) 1939.

Liber reports the case of a woman aged 43 who died of lobar pneumonia and terminal septicemia and meningitis. At necropsy the pineal body was observed

to be enlarged by a cyst measuring 14 by 11 by 9 mm. and containing a semisolid, grayish, gelatinous material. The cyst was lined partially with fibrous glia and with a single layer of columnar cells, which were continuous with the parenchyma and were situated on a collagenous basement membrane. The glial investment of the cyst was continuous with a glial mass which obliterated the pineal recess. There appeared to be no satisfactory explanation for the formation of the cyst or the origin of the fluid contents. A coincident observation was a greatly dilated cavum septi lucidi.

MACKAY, Chicago.

COAGULATION NECROSIS IN THE CENTER OF AN AREA OF SOFTENING IN A SENILE BRAIN. J. LEY, J. belge de neurol. et de psychiat. **39**:18 (Jan.) 1939.

Ley describes an area of coagulation necrosis which occurred in the center of an area of softening in the brain of an elderly person who had had an apoplectic attack followed by right hemiplegia and aphasia. Post mortem, an area of softening was observed in the left cerebral hemisphere in the distribution of the second branch of the middle cerebral artery. In the center of this was an area of coagulation necrosis. This form of degeneration is rare; Ley believes that it represents ischemic degeneration of the cerebral parenchyma due to an area of relatively increased anemia within the larger area of softening.

DE JONG, Ann Arbor, Mich.

CHANGES IN THE BRAIN IN EXPERIMENTAL PHOSPHORUS POISONING. TAKEYA-SIKO, Arch. f. Psychiat. **109**:113 (Jan.) 1939.

Takeya carried out experiments on dogs which were subjected to the effects of an 8 per cent mixture of yellow phosphorus. Severe hemorrhages were observed. There was no tendency to fatty degeneration. The large pyramidal cells showed so-called fissuration in some cases. In other cases there occurred fading of the large and middle-sized ganglion cells, which was regarded as an advanced stage of vacuolar degeneration due to the direct effect of the poison. A large number of small foci of necrosis developed in the brain, affecting chiefly the cells, but sometimes also the white matter. These were probably caused by the poison, but one cannot entirely rule out the possibility that they could be produced by secondary circulatory disturbances.

W. MALAMUD, Worcester, Mass.

COMPARATIVE PATHOANATOMIC INVESTIGATIONS OF THE BRAIN, WITH SPECIAL REFERENCE TO SENILE CHANGES. W. MÜLLER, Arch. f. Psychiat. **109**:147 (Jan.) 1939.

Müller studied 6,000 sections of the brains of human subjects, cats, horses and dogs to ascertain the changes that occur with old age. The study was made primarily with silver impregnations and fat stains. Of the 221 human brains, 118 showed senile plaques and fibrillary changes. Twenty brains were those of persons 90 years of age or over and showed these changes to a high degree. The author comes to the conclusion that in brains of persons between the ages of 85 and 90 histologic features of senile degeneration develop, regardless of the mental condition. The causes of these changes cannot be definitely established, but are probably manifestations of colloidal chemical processes. Some substance, which can only be described as soluble in xylene and acetone, seems to be of etiologic importance in this connection.

In the brains of 40 dogs, 13 cats and 6 horses the silver stains did not show any typical senile changes. The fat stains, however, showed an increasing deposit of pigment in the ganglion cells in keeping with the age of the animal. Of particular interest is the fact that in the dogs and cats, as contrasted with horses and especially with human beings, there was usually a marked increase in the

lipoid content. In the cats, calcification was frequent and was similar to that found in the human subjects. In 1 cat the development of a glioma could be demonstrated. Dogs, horses and cats do not live as long as human beings, and therefore there is not sufficient time for the development of senile changes.

W. MALAMUD, Worcester, Mass.

GANGLIONEUROMA OF THE CEREBELLUM. H. HEINLEIN and FALKENBERG, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:128 (March) 1939.

Ganglioneuroma of the cerebellum is extremely rare. Only 3 other cases have been recorded, namely those of Bielschowsky and Simons (*J. f. Psychol. u. Neurol.* **41**:50, 1930), Lhermitte and Duclos (*Bull. Assoc. franç. p. l'etude du cancer* **9**:99, 1920) and Schmidt (*Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres* **23**:594, 1926). Heinlein and Falkenberg report a case in a farmer aged 23. The onset of the illness, over two years before, was with unsteadiness of gait. Tinnitus, dizziness and headache soon appeared. The disease became progressively worse, so that the patient had to give up work after two years. The condition had become particularly bad during the three weeks before admission. The defect in gait became worse; pains in the back of the neck and vomiting appeared. The tinnitus on the left side became continuous, and hearing became defective on that side. The patient also complained of defective vision on the left side.

Examination showed weakness of the left side of the face, with deviation of the tongue to the left; the right pupil was wider than the left and was somewhat irregular; the pupillary reaction to light and on convergence was less brisk on the right. There was limitation of movement of the left eyeball in looking to the left, with diplopia on left lateral gaze. Horizontal nystagmus was elicited, with a coarse component on looking to the right. The right corneal reflex was absent; the palate moved up and to the left; the gag reflexes could hardly be elicited. There was some hypotonia on the right side; the knee jerk was pendular on the left; there were finger to nose ataxia and definite dysdiadokokinesis on the right side. The patient fell to the left and backward on closing the eyes; both arms, but especially the right, showed outward deviation; the head was tilted to the left; he walked with a wide base and showed marked unsteadiness on sudden turning. There was papilledema bilaterally. Otologic examination showed no evidence of labyrinthine involvement.

Autopsy showed enlargement of the vermis and the right cerebellar hemisphere. Except for the increase in size these parts appeared normal. Cross section of the affected parts of the cerebellum showed hardly any medullary layer. The granular layer was almost absent, and the cortex, or molecular layer, seemed exceptionally wide. There were numerous ganglion cells in the apparently widened molecular layer. These varied in maturity and size. Normal Purkinje cells, as well as very large cells with occasionally two or more nuclei, were seen. Small ganglion cells with round nuclei (neuroblasts) were also present. Intact granular cells were noted here and there. A number of the ganglion cells were found scattered even among the fibers of the medullary layer. The molecular layer was very rich in myelinated fibers. These were the axons of the neuroblasts in the granular layer. There were no myelinated fibers in the granular layer. Small collections of glia cells were seen in the molecular layer. There were no Alzheimer cells. Pseudocalcium was present around some of the capillaries in the molecular layer.

SAVITSKY, New York.

PATHOLOGIC CHANGES PRODUCED BY METRAZOL. K. MIYASHITA, Psychiat. et neurol. japon. **43**:2 (Jan.) 1939.

Miyashita studied the brains of rabbits after metrazol convulsions. He found changes of the acute or subacute type of Nissl in the ganglion cells. These changes were diffuse, but involved all parts of the cortex. No hemorrhages or softenings

were observed. The vessels were congested, but otherwise were not abnormal. There were no changes in the neuroglia, except hypertrophy of the astrocytes, giving rise to giant cell types.

ALPERS, Philadelphia.

Meninges and Blood Vessels

LYMPHOCYTIC CHORIOMENINGITIS. T. E. MACHELLA, L. M. WEINBERGER and S. W. LIPPINCOTT, Am. J. M. Sc. **197**:617 (May) 1939.

The authors describe the case of a white boy aged 14 with the signs and symptoms of meningitis, who died twenty days after admission to the hospital. The symptoms began ten days before hospitalization. The white corpuscles numbered 9,360, 79 per cent of which were neutrophils. The spinal fluid was cloudy, with a pressure of 120 mm. of water and 556 cells per cubic millimeter, all of which were lymphocytes. The essential pathologic changes consisted of marked thickening of the meninges, due to proliferation of connective tissue, with obliteration of the subarachnoid spaces. The meninges were infiltrated with lymphocytes, red blood cells and macrophages. The ependyma of the entire ventricular system was the site of an intense inflammatory reaction characterized by perivascular lymphocytic infiltrations, glial proliferations, engorgement of the vessels and hemorrhages. The choroid plexuses were partly necrotic and heavily infiltrated with inflammatory exudate. The cortex, basal ganglia and subcortical white matter were on the whole unaffected. Death was due to respiratory failure secondary to increased intracranial pressure, as the result of blockage of subarachnoid spaces at the base of the brain. The clinical picture, the similarity of pathologic changes to those observed experimentally in monkeys and the death of 2 guinea pigs, with no evidence of tuberculosis, following inoculation with spinal fluid, made the authors believe that the condition falls under the classification of acute lymphocytic choriomeningitis.

MICHAELS, Boston.

HEMOLYTIC STREPTOCOCCIC MENINGITIS OF OTITIC ORIGIN IN A YOUNG WOMAN AT TERM. SAMUEL T. BUCKMAN, Arch. Otolaryng. **29**:853 (May) 1939.

Buckman reports the case of a pregnant woman with meningitis who was treated successfully and was delivered of a healthy child. At admission the spinal fluid contained 2,000 cells. The next day there were 7,300 cells; subsequent taps showed a decrease in the number of cells. A hemolytic streptococcus was cultured from the spinal fluid. Culture on the eighth day gave negative results. A simple mastoidectomy was performed. Culture of the pus from the tip yielded hemolytic streptococci. Ten grains (0.65 Gm.) of sulfanilamide and 10 grains of sodium bicarbonate were given every two hours day and night, except when the patient was delirious, when from 5 to 10 cc of prontosil (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid, previously known as prontosil soluble and now to be called neoprontosil) was given intramuscularly. After three days the dose was reduced; administration of the drug was stopped on the thirteenth day of the illness. The patient received seven plain transfusions and two immunotransfusions. Two days after admission she was delivered of a normal baby, weighing 7 pounds 8¼ ounces (3,409 Gm.). The baby voided pink urine, showing the presence of sulfanilamide in the system. After the first two days a deep, severe jaundice, lasting eight days, developed in the child, but he was otherwise unaffected. The mother's condition continued to improve. She was allowed out of bed on the seventeenth postoperative day and was discharged on the twenty-first day, with a dry ear and good hearing.

HUNTER, Philadelphia.

INFLUENZAL MENINGITIS WITH RECOVERY. JOHN E. BROWN JR., HERBERT D. EMSWILER and LAWRENCE E. RECK, Arch. Otolaryng. **29**:860 (May) 1939.

A few cases of influenzal meningitis have been reported in which treatment with sulfanilamide was successful. The authors report a case of influenzal menin-

gitis with recovery after treatment with mastoidectomy, prontosil (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid, previously known as prontosil soluble and now to be called neoprontosil) solution, sulfanilamide by mouth and continuous spinal drainage. No specific serum was used. A white boy aged 6 years was admitted to the hospital with a diagnosis of acute mastoiditis and possible meningitis. The right mastoid was tender but not swollen. A roentgenogram showed that both mastoids were involved. Bilateral myringotomy was performed. Smears of the fluid obtained by lumbar puncture revealed organisms. Right mastoidectomy was done on the day of admission. Continuous spinal drainage was instituted, and prontosil solution was given intramuscularly. The patient made an uneventful recovery. Pleomorphic organisms were cultured both from the mastoid secretion and from the spinal fluid. The authors believe that chemotherapy may have been of some benefit and that there were no "untoward consequences from its use." HUNTER, Philadelphia.

MENINGOCOCCIC MENINGITIS: REPORT OF TWENTY-SEVEN CASES TREATED WITH SERUM AND SULFANILAMIDE. E. P. CAMPBELL, M. Ann. District of Columbia **8**:132 (May) 1939.

Campbell gives the essential features of the 27 interepidemic cases of meningococcic meningitis in the Walter Reed General Hospital from October 1935 to November 1938. The treatment given in the 27 cases consisted of antimeningococcus serum, antitoxin and sulfanilamide. Serum was administered intravenously and intraspinally immediately after the necessary sensitivity tests had been performed. Soon after the first spinal drainage, 100 cc. of serum diluted with 200 or 300 cc. of physiologic solution of sodium chloride was given slowly intravenously. The average amount of serum given in this manner to 22 patients was 221 cc., with extremes of 45 and 705 cc. Serum, warmed, undiluted, was given intraspinally by the gravity method and in amounts of from 5 to 10 cc. less than the quantity of spinal fluid withdrawn. Serum was given intrathecally to 18 patients in an average total amount of 106 cc., with extremes of 15 and 340 cc. Antitoxin was given to 3 patients before they were admitted to the hospital. Sulfanilamide was administered to 7 patients in an average total dose of 32.5 Gm., with extremes of 9 and 60 Gm. Five were given both serum and sulfanilamide, while 2 were given sulfanilamide alone. One of the former group died after receiving 14.5 Gm. of sulfanilamide and 100 cc. of serum. A subarachnoid block developed. Sulfanilamide is best employed by mouth if the patient is not vomiting. Otherwise it can be given subcutaneously, as outlined by Schwenkter. There were 36 complications in the entire series, including deafness, transient paralyses of the sixth and seventh nerves, arthritis, optic neuritis, paraplegia, endocarditis, subarachnoid block and panophthalmitis. Five deaths occurred, 2 from acute fulminating meningococcemia and 1 from status thymicolymphaticus. The author believes that the most effective form of treatment was intravenous and intraspinal administration of antimeningococcus serum in conjunction with sulfanilamide orally and/or subcutaneously. J. A. M. A.

"BENIGN" LYMPHOCYTIC MENINGITIS. J. E. SKOGLAND, Minnesota Med. **22**:462 (July) 1939.

Skogland reports the 10 cases of lymphocytic meningitis that have been observed at the University of Minnesota Hospital within the last ten years. In 1 of these antibodies against the virus of lymphocytic choriomeningitis were demonstrated in the blood serum. The disease in this case cannot be considered "benign," as it has run an active course for a year. In 3 of the other cases the neutralization tests were made on the serums five months, one year and two years, respectively, after recovery, with negative results. In the other cases the duration

was brief (several days or a few weeks); complications were typically absent. The syndrome is characterized by symptoms of meningeal irritation and lymphocytosis in the spinal fluid. Because of the case in which antibodies against the virus of lymphocytic choriomeningitis were present in the blood, the author suggests that the term "lymphocytic meningitis" replace that of "benign lymphocytic meningitis," which is in common use.

J. A. M. A.

CLIMATE AS A FACTOR IN EPIDEMIC MENINGITIS IN KORDOFAN. N. L. CORKILL, Lancet **1**:1203 (May 27) 1939.

Since clouds and a high humidity reduce ultraviolet radiation, the decrease in the number of cases of cerebrospinal meningitis under these climatic conditions seems significant. The onset of epidemics of this disease in the spring or at a time when there is a low vitamin A content of the food intake as well as an abundance of sunlight is, according to the author, a commanding correlation. The inference is that "susceptibility to meningitis is in the nature of a deficiency condition and is accentuated by exposure to ultraviolet rays." To strengthen this point, mention is made of the increase of cases of scurvy, keratomalacia and meningitis in Scandinavia during the spring. Corkill emphasizes the fact that persons trying to establish adequate quarantine measures should not lose sight of the importance of prolonged exposure to sunlight.

KRINSKY, Boston.

INTRAORBITAL ARACHNOIDITIS. REDSLOB, Rev. d'oto-neuro-opht. **17**:161 (March) 1939.

In recent years so much has been heard about optochiasmatic arachnoiditis that Redslob questioned the propriety of the term arachnoiditis. He made histologic studies of the intraocular arachnoid in specimens from 7 persons: 1 normal person, 4 patients with optic neuritis, 1 with meningitis and 1 with papillary edema due to extension of infection from suppuration of the sphenoid sinus. He concluded: (1) The arachnoid may be the seat of isolated inflammation, without participation of either the dura or the pia mater. (2) In all cases observed, the arachnoiditis was secondary to inflammation in the trunk of the optic nerve, or higher in the brain or the sphenoid sinus. Optochiasmatic arachnoiditis is probably secondary to inflammation of the cerebral substance. It is doubtful whether the arachnoid can be the primary seat of inflammation. (3) Inflammation of the dura does not necessarily extend to the arachnoid, although involvement of the latter may be associated with a sclerotic process in the leptomeninges. (4) Arachnoiditis provokes adhesions of the three cerebral envelopes, interrupting the flow of fluid in the intervaginal spaces.

DENNIS, San Diego, Calif.

MASTOIDITIS AND CHRONIC OSTEOMYELITIS ON THE RIGHT SIDE, PROVOKING REPEATED ATTACKS OF MENINGITIS. F. ODY, Rev. d'oto-neuro-opht. **17**:164 (March) 1939.

Ody reports a case of acute meningitis and petrositis, with sequester formation, in a man aged 39. At the age of 2 years he had had an attack of acute mastoiditis on the right side and was treated by antrotomy. In 1912 he suffered from lancinating pains in the same mastoid. In 1920 he had headache, vertigo, vomiting and falling to the left; he was given antisyphilitic treatment. In 1934 an attack of acute meningitis occurred, and pneumococci were found in the spinal fluid. In May 1935 there developed another attack of meningitis, and the right mastoid was exenterated. In November 1935 another attack of meningitis occurred, and in December, still another. Roentgenograms revealed osteomyelitis and sclerosis of the petrous bone, with sequester formation. In February 1936 three operations on the petrous bone were undertaken, and part of the necrotic bone was removed, a sequester within the dura being left. The patient made a prompt recovery.

A lumbar puncture made in June yielded fluid with a normal formula. In February 1939 the patient was still in good health. The presence of osteitis on the posterosuperior surface of the petrous pyramid indicated that the meningeal infection was transmitted via the vestibular aqueduct. The persistence of almost normal hearing and of part of the labyrinthine function on the diseased side suggests that the infection was propagated not by the internal ear, but by the venous channels of the bone.

DENNIS, San Diego, Calif.

Diseases of the Brain

HUMAN EQUINE ENCEPHALOMYELITIS. R. N. LARIMER and E. G. WIESSER, J. Iowa M. Soc. **29**:287 (July) 1939.

Larimer and Wiesser state that during August and September 1938 16 patients presenting features of meningitis, but with unusual changes in the spinal fluid, were seen in St. Joseph's Hospital. In 11 the condition was characterized by a sudden onset with headache and fever. The remaining patients had indefinite complaints of headache or fatigue for as long as seven days before calling their physician. Headache, stiff neck and a positive Kernig's sign were relatively constant, and usually pathologic reflexes were transient. Changes in the spinal fluid included an increase in the cell counts, especially in the lymphocyte series, normal or increased sugar content and the absence of organisms in smears and cultures. The course characteristically was short, the fever remaining high for about five days. No relation between severity of symptoms, physical signs or spinal fluid changes and the mortality rate was noted. Cells in the spinal fluid were no more numerous in the 4 cases in which the termination was fatal than in the 12 cases in which recovery occurred. The 12 patients who recovered showed no sequelae at the time of dismissal. The histories in these cases reveal the close resemblance to epidemic encephalitis, human equine encephalomyelitis, benign lymphocytic meningitis, choriomeningitis, polioencephalitis and other conditions. Infection in more than one member of a family was not encountered. As the area from which the cases of this report came has had an epidemic of "equine encephalitis," with definite exposure to horses so affected in 6 of the 10 cases reported, it seemed probable that the disease in the present cases was caused by a similar infective agent. However, the authors state that they have no proof for this impression. Treatment in these cases consisted chiefly of repeated spinal punctures and other means of reducing intracranial pressure. Fluid in amounts of from 50 to 100 cc. was given intravenously. Sulfanilamide was given an intensive trial, but did not seem to alter the course of the disease. Morphine in large doses provided the best means of relief from headache. Moderately large doses of magnesium sulfate by mouth or rectum seemed to have a favorable effect. Autohemotherapy in 1 case seemed valueless. Convalescent serum was not tried, but would deserve trial if one were sure of the diagnosis.

J. A. M. A.

INTERPRETATIONS OF FUNCTIONS OF FRONTAL LOBE BASED ON OBSERVATIONS IN FORTY-EIGHT CASES OF PREFRONTAL LOBOTOMY. W. FREEMAN and J. W. WATTS, Yale J. Biol. & Med. **11**:527 (May) 1939.

During the last three years Freeman and Watts studied 48 patients who have been subjected to prefrontal lobotomy because of certain disabling neurotic and psychotic states. The operation is not a shocking procedure and is relatively painless, so that the authors have been able to carry out a number of observations while the patients were under local anesthesia. The more cooperative patients have undergone fairly comprehensive psychologic tests both before and at intervals after the operation, so that both the immediate and the remote effects of the operation are known. The authors conclude that the frontal lobes are concerned with the projection of the individual as a whole into the future, with the forma-

tion of an image of the individual as he is becoming. The other suggested functions appear to be mechanisms by which this is attained. Many of the symptoms of disease of the frontal lobes can be explained on the basis that the individual has lost his power of self criticism, is more easily satisfied, is lacking in "social sense" and has had impairment of imagination as related to himself. The frontal lobes are not centers of intelligence or of emotion, nor are they directly concerned with the energy drive of the individual. They assemble the available data, synthesize them, plan a course of action with the ideal in mind and, equipped with energy of response and with approriate effective tone, project the individual into the future, direct him toward his goal—and criticize his shortcomings.

J. A. M. A.

PITUITARY ADENOMAS: FOLLOW-UP STUDY OF SURGICAL RESULTS IN 338 CASES (DR. HARVEY CUSHING'S SERIES). W. R. HENDERSON, Brit. J. Surg. **26**:811 (April) 1939.

Henderson reports the surgical results in 338 cases of histologically verified pituitary tumors observed at the Brigham Hospital during a period of twenty years. The report deals principally with surgical mortality statistics, the early results of operation and a follow-up study of the patients, the last of whom underwent operation on July 23, 1932. Only 3 of the 338 patients have not been heard from since their discharge from the hospital. There were 260 chromophobic adenomas (including 32 mixed adenomas), 67 acidophilic adenomas and 11 adenocarcinomas. No example of a basophilic adenoma has been identified. The incidence of pituitary adenomas in Cushing's series of 2,023 verified intracranial tumors is 17.8 per cent. Chromophobic adenomas produce only local compression effects, whereas acidophilic adenomas evoke general constitutional disturbances, and often local effects in addition. The adenocarcinomas are apt to infiltrate surrounding structures. The late results, analyzed on the basis of the duration of improvement after operation, indicate great variability in the rate of growth and behavior of the chromophobic adenomas. After a successful transphenoid operation without irradiation, some patients had no further trouble for as long as twenty years. On the other hand, rapid recurrence within two or three years may take place even after a far more radical transfrontal operation plus roentgen treatment. While many patients maintained this improved status for from ten to twenty years, 95 per cent of those who had a recurrence showed indications of it within five years after operation. The clinical course of acidophilic adenomas differs from that of the chromophobic adenomas. The two types of symptoms—local pressure (visual) effects and system effects—frequently show spontaneous remissions and exacerbations and often respond differently to treatment. Operation usually produces marked improvement in vision but may have no effect on the severe headaches, especially in cases in which there is a small tumor. The systemic disturbances are ultimately apt to be the most serious because of the deleterious effects of the hormone secretion on the cardiovascular system and on sugar metabolism. The operative mortality is slightly higher than for the chromophobic adenomas, but the late surgical results appear to be better. The acidophilic tumors are more amenable to roentgen therapy. The adenocarcinomas have not yet been subjected to sufficiently thorough pathologic study. Clinically, some of them behave like chromophobic adenomas; others, however, are hopelessly malignant, infiltrate the base of the skull and produce multiple cranial nerve palsies. J. A. M. A.

LISSAUER'S DEMENTIA PARALYTICA. P. DIVRY, J. belge de neurol. et de psychiat. **39**:5 (Jan.) 1939.

Divry describes a case of Lissauer's dementia paralytica in a man aged 32. The report is significant in that there was observed extensive atrophy of the entire right cerebral hemisphere. Not only were the frontal, parietal, temporal and occipital lobes involved, but contraction of the ventricle and reduction in the amount of the white matter were also present. DE JONG, Ann Arbor, Mich.

DIFFERENTIATION OF ALZHEIMER'S AND PICK'S DISEASE. P. DIVRY, J. belge de neurol. et de psychiat. **39**:238 (April) 1939.

Divry reports the case of a patient whose clinical manifestations suggested Pick's disease but whose condition was diagnosed as Alzheimer's disease at autopsy. The patient was a man aged 58, whose family history revealed nothing of significance. The principal mental symptoms were inertia and indifference, motor and amnesic aphasia and a tendency to mutism. There was relative preservation of gnostic and praxtic functions, with absence of motor phenomena, hallucinations and delirium. The pathologic changes were characteristic of Alzheimer's disease.

DE JONG, Ann Arbor, Mich.

RAPIDLY FATAL ENCEPHALITIDES IN CHILDREN. C. GARDÉRE, M. DAUVERGNE and G. BERTRAND, J. de méd. de Lyon **20**:281 (May 5) 1939.

Gardére and his associates point out that certain acute encephalitides in children are noteworthy for their particularly rapid development and their exceptional gravity. The encephalitides with rapidly fatal termination are those in which the evolution does not go beyond the third day. They seem to appear especially in nurslings. Of 43 cases, 17 concerned infants of the first year, 9 those of the second year and the other 17 children between the ages of 2 and 12 years. This encephalitis with rapid death is most frequently of the parainfectious type (34 of 43 cases). Whooping cough seems to be the most frequent causal infection during the first two years of life, and measles, during the later years. Varicella and vaccinia are less often the cause. In some cases the cerebral infection seems to be primary and the cause is still obscure, but at times it may be of influenzal origin and in other cases a connection with lethargic encephalitis may be considered. The symptomatology is characterized chiefly by convulsions, somnolence and coma. What is especially characteristic of these forms is the almost immediate appearance of symptoms indicating bulbar involvement: irregularity of the respiratory rhythm and tachycardia. Lumbar puncture usually yields a normal cerebrospinal fluid or one with slight lymphocytic reaction. The anatomopathologic studies are as yet few, but they reveal the usual diffuse lesions of encephalitis with involvement of the bulbar centers, where cytologic lesions are found in spite of the rapidity of evolution. The diagnosis is especially difficult in the primary forms. In nurslings the possible existence of suppurating otitis or mastoiditis must be considered, for these may produce similar symptoms. The outcome of the peracute forms of encephalitis is usually rapidly fatal, although occasionally the bulbar symptoms subside and the child recovers.

J. A. M. A.

ABSCESS OF THE RIGHT FRONTAL LOBE REVEALED BY TRAUMA OF THE LEFT ORBIT. A. BARRAUX, P. ROQUES and J. E. CAMBASSÉDÈS, Rev. d'oto-neuro-opht. **17**: 336 (May) 1939.

The authors report the case of a man aged 22 who experienced headache, vertigo and bradycardia after a fall and blow to the region of the left orbit. The spinal fluid was slightly tinged with blood. Roentgenographic examination revealed no evidence of fracture and very slight clouding of the right nasal sinuses. After several episodes of return of the headache and bradycardia, each time relieved by spinal puncture, there developed euphoria and the patient escaped from the hospital. The morning after leaving the hospital he suddenly fainted and died within a few minutes. There had been no rise of temperature and no neurologic signs except paresis of the left sixth nerve and bilateral papillary stasis, which developed shortly before death. Autopsy revealed a fracture of the roof of the left orbit, at which point the congested frontal lobe was adherent. The right frontal lobe was increased in volume, was not adherent and contained a large abscess with a thick capsule. The cortex and ventricles were normal. Inquiry revealed that the patient had complained for a long time before the accident of rhinorrhea, accompanied by

intermittent headaches in the right frontal region. It was also learned that at the time of the accident the patient had been wounded in the left oribital region by a blow from a bayonet during a friendly scuffle. The authors believe that the abscess was secondary to the low grade of sinal infection and had developed over a period of several months, giving time for formation of the capsule. The trauma was regarded as an important contributory factor, in that it upset the cytoarchitectonics and myeloarchitectonics in a region rendered vulnerable by the presence of the abscess.

DENNIS, San Diego, Calif.

CLINICAL PROBLEM OF MIGRAINE IN CHILDREN. A. OLIVEIRA LIMA, Brasil-med. **53**:765 (July 29) 1939.

According to Oliveira Lima, allergy is the main etiologic factor producing migraine in children. Of secondary importance are heredity and constitutional physical factors, or pathologic factors. The condition is more frequent in girls than in boys and, again, is more frequent in girls of a nervous type than in normal girls. The clinical symptoms are those of the prodromal and aural periods, the attack and the after-attack period. The topographic pattern, acuteness and evolution of the disease vary in the different cases. The main symptom of the attack is the unilateral headache, which appears at regular or irregular intervals with pain of the oppressive, irradiating or neuralgic types and is accompanied by nausea, vomiting and various sensory disturbances. Intolerance to light is more or less acute in all cases. The after-attack stage gradually establishes itself, after aggravation of the acute symptoms of the attack. It becomes evident by appearance of physical depression, sleep, disturbances in the secretion and elimination of urine, rhinorrhea and general dull pain. In some cases the development of an abortive or equivalent attack prevents occurrence of typical attacks. Chronic headache may be a late sequel of the disease. Treatments are of three types: (1) preventive, (2) symptomatic and (3) after-attack. There are two forms of preventive treatment: that in which patients are advised not to marry persons who are sensitive to the same allergens, and the actual preventive treatment of the patient, which includes proper diet and avoidance of food and ambient allergens to which the patient is sensitive. Symptomatic treatment varies with the type of headache. The following general measures are indicated: The patient is confined to a dark quiet room, and drugs with a vasodilating action are administered during the prodromal and aural stages; during the attack, according to indications, drugs of vasoconstrictive action, or else analgesics, sedative drugs and especially ergotamine tartrate, are given. Caffeine, calcium and some other drugs can be resorted to when indicated. The after-attack treatment is a continuation of the symptomatic treatment with certain modifications. It consists of the proper diet, rest and administration of either sedatives or stimulants, according to indications.

J. A. M. A.

CRANIAL INJURIES. D. KULENKAMPFF, Beitr. z. klin. Chir. **169**:414 (May 31) 1939.

For the sake of clarity in the discussion of injuries to the brain, Kulenkampff limits himself to the terms concussion and contusion. Concussion is manifested by a brief period of loss of consciousness, frequently associated with vomiting, and a headache which disappears in the course of a few hours or a few days. The lumbar puncture alone can determine whether tearing of the cerebral blood vessels has taken place. In contusion there is trauma of the brain tissue causing swelling and rise in the intracranial pressure. As a rule, there is blood in the cerebrospinal fluid, the pressure of which rises with the gradual development of the reactive swelling of the brain. The rise in the pressure of the cerebrospinal fluid makes it possible in many instances to estimate the compensatory capacity, as expounded by Kocher and by Cushing. Two cases are cited in which the cerebrospinal fluid pressure equaled 400 mm. In the first case removal of 5 cc. reduced the pressure

to 200 mm., while in the second it was necessary to remove 10 cc. to bring it down to 200 mm. The compensatory capacity in the first case was more pronounced than in the second. The anatomic structures involved in the compensatory phenomenon are the sinuses, the veins, the ventricle system of the brain and the numerous large lymph spaces, on the one hand, and the development of the cranium and the constitutional type of variations of the anatomic structures mentioned, on the other. For consideration of the intracranial pressure the anatomic division of the cranial cavity into three parts is confusing; the author prefers to speak of the anterior and posterior areas of pressure. Repeated lumbar punctures are essential for recognition of the type of injury and the therapeutic indications. The fear of renewed hemorrhage as the result of lowered pressure is without foundation. The numerous symptoms resulting from cranial injuries are principally the result of inadequate regulation of the circulatory systems. This is demonstrated by the immediate improvement in some of the cases brought about by one or two late spinal punctures. The author believes that the number of late complications could be materially lowered by continuing the original treatment to the point of restoring the patient to full working capacity.

J. A. M. A.

Poisoning with Tetraethyl Lead Gasoline and Its Oxidation Products. E. Störring, Deutsche Ztschr. f. Nervenh. **148**:262, 1939.

Störring describes 2 cases of chronic intoxication with tetraethyl lead gasoline. In the first case only stippling of the erythrocytes was present; clinically, there were generalized epilepsy and extreme nervous irritability. These symptoms occurred about two months after the patient had started to clean the motors of airplanes with tetraethyl lead gasoline in closed rooms. The amount of lead in the blood was increased to more than twice the normal limit. He was exposed to the lead for one and one-half years; he recovered completely soon after his removal from the noxious environment.

Another patient worked in a gasoline station for one and one-half years. One year after exposure to the lead he started to lose weight rapidly, became depressed and suffered from insomnia. One and one-half years after removal from his place of work, he suffered three attacks of generalized epilepsy. Störring attributed these to the lead poisoning, although, except for a slight increase in the lead content of the blood, no signs of lead poisoning were present. Three additional cases are reported in which the noxious agents were the oxidation products of tetraethyl lead, particularly lead bromide. Two of the patients had to clean motor cylinders, whereas the third, an aviator, was not in direct contact with tetraethyl lead gasoline or its oxidation products. The author assumes that in this case inhalation of gases from the exhaust pipe caused the lead intoxication. The author points out that 4 of the 5 patients had been sick for some time without lead poisoning having been recognized as the cause of the illness.

Adler, Boston.

Treatment, Neurosurgery

Alcohol-Tobacco Amblyopia Treated with Thiamin Chloride. Lorand V. Johnson, Arch. Ophth. **21**:602 (April) 1939.

Toxic amblyopia, with centrocecal scotomas and relatively large scotomas for red and green, and commonly with peripheral neuritis and hypochlorhydria, appears to be associated with deficiency of the vitamin B complex. Johnson reports the effect of treatment of 5 patients with alcohol (toxic) amblyopia with thiamin chloride and nicotinic acid. Two of the patients made a complete recovery with abstinence and the use of thiamin chloride. A third had used both alcohol and tobacco to excess. With similar treatment the vision of a fourth patient improved from 20/70 and 20/100 to 20/40, with a narrow scotoma remaining for red and

green. In the fifth patient, who at the onset of treatment already had atrophy of the papillomacular bundle, the condition progressed to complete atrophy of the optic nerve despite the use of both thiamin chloride and nicotinic acid.

SPAETH, Philadelphia.

FARADIC SHOCK TREATMENT OF "FUNCTIONAL" PSYCHOSES. N. J. BERKWITZ, Journal-Lancet **59**:351 (Aug.) 1939.

Since complications such as dislocations and fractures occur in insulin and metrazol shock therapy and because of the terror and apprehension of the patient toward the treatment, Berkwitz offers faradic shock as a probable substitute. He tried this form of treatment in 4 cases of "functional psychoses" with encouraging results. Because of the small number of patients treated and the short period for observations, no definite conclusions are formed. It may be possible that this method may be an adequate substitute for the more drastic forms of shock therapy being used today. The maximal voltage produced was approximately 20,000 volts. One electrode was placed on the forehead and the other on the nape of the neck. The patient's breakfast was withheld and an enema was given before commencement of the treatment. From five to ten shocks of one second's duration each were given, with an interval of one second between shocks. Such current can be safely tolerated by patients having no vascular disease. The patient's eyelids and facial muscles twitched, the head jerked, and evidence of fear and pain was exhibited. The patient did not appear to be in mental anguish or to have the violent jerking seen in convulsions. Immediately after the electrical shocks were given, from 4 to 7 cc. of a 5 per cent solution of pentothal sodium was injected intravenously to produce prompt sleep. Surgical anesthesia was attained in about thirty seconds. Unconsciousness lasted for several minutes, depending on the amount of the drug administered. Respiration must be watched closely. By the administration of an inhalant, such as spirit of ammonia, the patient may be kept awake. Thus, the interviewer often may gain much information of the content of the patient's thought which is not obtainable at other times.

J. A. M. A.

SURGICAL TREATMENT OF EPILEPSY. R. M. STUCK, Rocky Mountain M. J. **36**: 547 (Aug.) 1939.

Stuck suggests that many chronic epileptic patients when studied carefully will be found to have definite surgical cerebral lesions. These focal lesions, which are varied in nature, are so situated that they are irritating to the cortex. In some cases the lesion is a contracting scar from an old compound fracture of the skull; in others it is a tumor, an abscess, old encephalitis, meningitis, a hemorrhage or the like. In order to determine the character and location of the focal lesion, a carefully taken history, with special reference to the sequence of events in the attacks, as well as an encephalogram or a ventriculogram, is essential. It may even be necessary for the physician to place the patient under observation in the hospital and to produce a few attacks in order that they may be accurately observed. Overfunction of the cerebral cortex usually results in an epileptic fit or convulsion. When there is a widespread disturbance, such as toxemia, the convulsion is generalized from the onset. Occasionally, however, the patient does not lose consciousness or have a generalized convulsion, although a generalized convulsion may develop later. In such a case it not infrequently happens that the patient experiences an initial localized movement or sensation, known as an aura or hallucination, which is followed by spread of the impulse over the body, like a ripple across a pool of water, until the whole body is affected, consciousness is lost and a major convulsion ensues. The most valuable study of the seizure is made in the period before consciousness is lost. By intimate questioning at this time it is possible to identify the manner of onset of the attack and to localize

grossly the cerebral focus. The initial event in the convulsion is a "signature" of the focus and is therefore the most important bit of information in the history. This "signature" may be manifest by numbness, tingling or a feeling of deadness of the finger, the hand or the foot; local weakness; a hallucination of smell, taste, odor or sight, as shown by flickering lights, or temporary inability to speak.

J. A. M. A.

QUININE IN MYOTONIA CONGENITA: ITS ANTAGONISM TO PROSTIGMIN. G. BRISCOE, Lancet **1**:1151 (May 20) 1939.

Briscoe carried out experiments in an effort to determine whether the characteristic depressant effects of prostigmine on normal muscle are antagonized by quinine as they are by curarine. Contractions of mammalian muscle (cat's quadriceps) have been recorded isometrically. Briscoe found that quinine, injected intravenously, is antagonistic to prostigmine and synergistic with curarine in its effects on normal skeletal muscle. Quinine produces its effects on muscle both by raising the threshold of the motor end plates and by direct action on the muscle fibers. It is not possible to decide which of these two actions of quinine is the more important in relief of the rigidity of congenital myotonia until more is known of the cause of this disease. It is suggested that in congenital myotonia there is hyperexcitability to normal amounts of acetylcholine.

J. A. M. A.

RADIOTHERAPY OF INTRACRANIAL TUMORS, WITH SPECIAL REFERENCE TO TREATMENT OF PITUITARY TUMORS. O. ORLEY, Proc. Roy. Soc. Med. **32**:1137 (July) 1939.

Orley reviews the results obtained in the roentgen treatment of intracranial tumors. He states that most of the gliomas are sensitive to roentgen rays but that the degree of sensitivity varies with the histologic type, in the descending order: medulloblastoma, ependymoma, astrocytoma and glioblastoma multiforme. The oligodendroglioma is resistant to roentgen rays. Of the vascular tumors, the hemangioblastomas should be treated by operation and postoperative irradiation, while the malformations should receive radiation alone. The meningiomas are resistant tumors. The evolution of pituitary adenomas can be divided into three stages: endocrine, visual and tumoral. The endocrine phase should be treated with radiation and the tumoral phase surgically, and the treatment of the visual phase should be determined by the circumstances. Patients undergoing roentgen therapy should be watched closely and surgical intervention undertaken when required. The best results follow combined treatment.

J. A. M. A.

ACCIDENTS IN THE COURSE OF METRAZOL THERAPY OF SCHIZOPHRENIC PATIENTS. M. GROSS and G. GROSS-MAY, J. belge de neurol. et de psychiat. **39**:336 (May) 1939.

Gross and Gross-May differentiate three groups of complications from insulin and metrazol therapy of schizophrenia. They first cite those of a mechanical nature which involve the osseous, tendinous and muscular systems. They show that these complications are explained by the mechanism of the epileptic crisis and the enormous muscular tension which it provokes. The second group of accidents are those involving the vascular system. In this connection the authors cite cases of arrhythmia, irregularities of the pulse, syncope and so on. They themselves observed auricular fibrillation which persisted for four hours. The third group of complications are pulmonary. The authors cite cases of respiratory arrest, pulmonary embolism and pulmonary abscess and say that, according to Ligterink, these accidents can be explained in three ways: (1) by thrombophlebitis resulting from intravenous injections (this seems the most probable course) and

followed by embolism, (2) by vascular spasms due to the specific action of metrazol and (3) by aspiration during the attack. In conclusion, the authors say that their enthusiasm for the new treatments for schizophrenia is impaired neither by reports of accidents nor by statistics on fatalities occurring in these treatments. Of 2,000 schizophrenic patients, half of whom had been treated with insulin, Malzberg found the mortality to be four times as great in the subjects who had not been treated as in those who had been treated. The authors conclude that they are justified in not letting the risk of death deter them from continuing the metrazol therapy of schizophrenia.

J. A. M. A.

TREATMENT OF POSTDIPHTHERITIC PARALYSIS WITH VITAMIN B_1. P. FEIGE, Fortschr. d. Therap. **15**:333 (June) 1939.

Reviewing 1,590 cases of diphtheria which were observed during the years 1936 and 1937, Feige found 100 cases in which postdiphtheritic paralysis developed. Paresis of the soft palate was observed in 90 cases, paresis of the ocular muscles in 20 cases, paralytic symptoms of the legs in 23 cases, paralysis of the pharyngeal muscles in 18 cases, paralysis of the respiratory musculature in 4 cases, paralysis of the musculature of the neck and back in 3 cases and paralysis of the diaphragm only once. Some of the children had more than one form of paralytic symptoms, and in 18 cases the paralysis threatened life. Of the 60 patients in whom the entire course of the postdiphtheritic paralysis could be observed, 30 were treated with a preparation of vitamin B_1 and 30 either received no treatment for the paralytic symptoms or were treated with other medicaments. A comparison of these two groups of patients revealed that in those who were treated with vitamin B_1 the paralytic symptoms persisted on the average for twenty-nine and six-tenths days, whereas in the other group they persisted on the average for forty-nine days. The author administered the vitamin B_1 by mouth and by intramuscular injection on alternate days. On one day the children were given three times 1 tablet containing 1 mg. of the vitamin, that is, 1,200 pigeon units; on the following day they were given an intramuscular injection of 1 cc. of a vitamin B_1 preparation which contained 4,000 pigeon units. In discussing the pathogenesis of postdiphtheritic paralysis, the author cites observations of several investigators and suggests that these postdiphtheritic paralytic symptoms are the result of the concurrence of toxic impairment of the tissues and lack of the B_1 substance, which has a ferment-like action. He thinks that this explains at the same time the success of the treatment with vitamin B_1.

J. A. M. A.

ROENTGEN THERAPY OF TRAUMATIC EPILEPSY. W. VON WIESER, Monatschr. f. Psychiat. u. Neurol. **101**:171 (June) 1939.

Von Wieser shows that traumatic epilepsy reacts to treatment with roentgen rays in the same manner as do the inflammatory and genuine forms, provided the cerebrum is irradiated by the direct method. If an attempt is made to treat epilepsy by the indirect method, it is necessary to differentiate between irradiations of the sympathetic system alone and of the medulla oblongata plus the sympathetic system. The first of these two indirect methods of roentgen therapy cannot be used either in traumatic or inflammatory epilepsy or in old cases of genuine epilepsy, whereas the second method can be used in all types of epilepsy. Since, however, experiences with the latter method are limited as yet, it is not known whether it will produce as satisfactory permanent results as does the direct method of roentgen treatment. Regarding the mode of action of the direct and the indirect method of roentgen therapy of traumatic epilepsy, the author says that the direct method tries to influence the cause of the disease whereas the indirect method aims to reduce the threshold for the stimuli that elicit the attacks.

J. A. M. A.

CLINICAL EXPERIENCES AFTER A YEAR'S TREATMENT OF PSYCHOSES WITH SO-CALLED METRAZOL SHOCK. V. HAHNEMANN, Ugesk. f. læger **101**:771 (June 29) 1939.

Hahnemann reports that in 151 (73 per cent) of the 207 cases of schizophrenia in which von Meduna's convulsion therapy was employed the duration of the psychosis had been from two to twenty-eight years. Full remission resulted in 40 cases and partial remission in 69. Of the 36 cases in which the disorder had existed for less than one year, full remission was attained in 25 (69 per cent) and partial remission in 6 (17 per cent), and there was no improvement in 5 (14 per cent). Treatment with metrazol was also given in 24 cases of depression and 15 cases of manic-depressive psychosis. Full remission occurred in all cases. The importance of carrying out a rational psychotherapy simultaneously with the shock treatment is stressed.

J. A. M. A.

Special Senses

THE OCULAR SYMPTOMS OCCURRING FROM MALNUTRITION IN HUMAN BEINGS. TOM D. SPIES, Am. J. M. Sc. **198**:40 (July) 1939.

Spies reports the cases of 50 patients with pellagra, beriberi and riboflavin deficiency who improved after the administration of synthetic nicotinic acid, synthetic thiamin hydrochloride and synthetic riboflavin. Nevertheless, they had or there developed ocular manifestations, characterized by severe burning, itching and excessive dryness of the eyes; often they spoke of a "scum" over the eyes. There were granulation and extreme redness of the conjunctiva, particularly of the lower lids, and a striking degree of photophobia. In 65 of 70 unselected cases in the nutrition clinic, there was a striking deficiency of vitamin A in the diets. Treatment in the form of carotene in oil or percomorph liver oil (vitamin A), in amounts ranging from 10,000 to 50,000 units, enabled these patients to read better; the burning ceased, and the conjunctivitis and photophobia disappeared.

MICHAELS, Boston.

LOCALIZING VALUE OF INCONGRUITY IN DEFECTS IN THE VISUAL FIELDS. DAVID O. HARRINGTON, Arch. Ophth. **21**:453 (March) 1939.

Asymmetry or incongruity of incomplete homonymous hemianopic defects in the visual fields is a constant finding with lesions of the anterior portion of the geniculocalcarine pathway. This defect becomes less and less evident the farther back the visual pathway is interrupted, until in cases of defects in the visual fields found in association with lesions of the occipital lobe the degree of symmetry is striking.

Harrington believes that quantitative perimetry is the only method of value in detecting the finer degrees of asymmetry in case of incomplete homonymous defects in the fields of vision. He finds that when this method is used lesions of the temporal, parietal and occipital lobes of the brain are seen to produce homonymous hemianopias, which when incomplete show varying degrees of asymmetry constant enough to be of localizing value. Harrington reports 8 cases of lesions of the temporal lobe and 2 cases of lesions of the occipital lobe to illustrate this fact. He believes that the cause of these characteristic defects is to be found in the dissociation in the temporal lobe of homonymous fibers from corresponding retinal points and their gradual coalescence in the postparietal area.

SPAETH, Philadelphia.

HALLUCINATIONS AND VESTIBULAR FUNCTIONS. LHERMITTE and BINEAU, Rev. d'oto-neuro-opht. **17**:241 (April) 1939.

Bonnier showed that disturbances of the equilibratory apparatus can cause curious modifications of the personality. It is easy to comprehend how false perceptions engendered by disorders of the vestibular apparatus have a special bear-

ing on the consciousness one has of the body, "the image of the corporeal me." Lhermitte and Bineau report 2 cases. The first patient had hallucinations of the corporeal schema and visual hallucinations, accompanied by intense vertigo, nystagmus, vomiting and a sensation of spatial displacement. To the second patient the head seemed not to be an extension of the body but to lie to one side. In both patients a lesion of the central vestibular apparatus was evident, and all symptoms were referable to the rhombencephalon. In Stenvers' case the visual hallucinations were due to a tuberculoma located in the pons, causing gross changes in the central vestibular pathways.

DENNIS, San Diego, Calif.

STRUCTURE OF THE HUMAN OPTIC CHIASM. P. QUERCY and R. LACHAUD, Rev. d'oto-neuro-opht. **17**:245 (April) 1939.

Quercy and Lachaud criticize the classic conception of the arrangement of the fibers in the optic pathways. The following facts are opposed to the classic doctrine: 1. Instead of a direct temporal bundle of fibers at the external angles of the chiasm, horizontal sections show a crossed temporal bundle passing from one optic nerve to the opposite optic tract. 2. The whole of the optic nerve contains, then, crossed fibers; but there are also found across the whole width of the nerve direct fibers given off from the bundles of the crossed axons, which pass to the optic tract of the same side. Thus, the optic nerve is arranged in a homogeneous manner of direct and crossed elements. 3. Each optic tract receives the crossed and direct fibers, which are distributed uniformly throughout its whole thickness.

The old theory of an inextricable mixture of fibers in the chiasm is supported by the following facts: 1. In the optic nerve and in the chiasm the nerve fascicles proceed with the most unexpected exchanges of place. 2. In sagittal sections the stratification of divided horizontal fibers is disturbed by ascending and descending fibers, which are, in a large part of the thickness of the chiasm, responsible for the layers and quadrants (superior and inferior) of the optic tract and, it seems, of the retina.

DENNIS, San Diego, Calif.

FANTOPSIAS OF TRUC. C. DEJEAN, Rev. d'oto-neuro-opht. **17**:248 (April) 1939.

Fantopsias were first observed by Bonnet in 1769 and were described by Truc in 1925. These experiences are not luminous scotomas, but are persons and objects, purely imaginative and do not correspond to anything in the visual fields. They occur in persons free from psychopathic states or focal lesions of the brain and are recognized by the patient as unreal. Amaurosis and amblyopia are not prerequisites to the development of fantopsias. Dejean reports 3 cases, all of elderly persons who were more or less mentally deficient and arteriosclerotic. They did not have mental disease. Fantopsias are complex, imagined creations. Excitation of the retina can produce phosphenes or deformation of real objects, but it cannot create images. It is only the cerebral cortex that can give rise to fantopsias. If softening, hemorrhage, vascular atresia or spasm occurs around the calcarine fissure, the images appear laterally and have a hemianopic distribution; if the hallucinations are a part of central vision, the lesion is probably in the parieto-occipital region or at the angular gyrus. Fantopsias are produced by derangement of cortical visual perception in predisposed subjects under the influence of an ocular lesion. The effect of amblyopia or deprivation of light in this connection is well known to oculists.

DENNIS, San Diego, Calif.

COLORED AUDITION. H. PROBY, Rev. d'oto-neuro-opht. **17**:261 (April) 1939.

The phenomena that constitute colored audition arise in the domain of vision and are provoked by sensations or ideas outside the ordinary laws of perception. They are simple luminous or colored impressions, symbols, diagrams or even

persons, of variable intensity or they may be merely an abstract notion of color. Colored audition (*synopsies*) is slightly more frequent in women; it may be acquired through examination which calls the patient's attention to the phenomenon, or it may be spontaneous. It is usually lasting, and while the manifestations may be diminished in frequency or intensity by age, they persist and are rarely modified. Colored audition arises frequently in young persons. Whether it occurs in youth or later as a result of external influences, a favorable terrain, prepared by heredity, is implied. Identical formulas are rare, although Lemaître reported the instance of a mother and child, in each of whom the vowels produced the sensation of the same colors. The study of colored audition in identical twins would shed additional light on the factor of heredity. Colored audition is not pathologic, but is found only in normal persons. DENNIS, San Diego, Calif.

HEMIACHROMATOPSIA WITH HEMIANOPIC HALLUCINOSIS. P. DELMAS-MARSALET and BESSIÉRE, Rev. d'oto-neuro-opht. **17**:274 (April) 1939.

Delmas-Marsalet and Bessiére report the case of a woman aged 67 who awoke one morning complaining of weakness in the right lower limb and disturbance in vision. From time to time she saw images of animals, moving from left to right, in the right half of each visual field. The hallucinatory phenomena occurred chiefly during rotation of the head or on transverse movements of the eyes. They did not occur when the eyes were closed. Examination revealed bilateral hemiachromatopsia, normal macular color vision and normal form fields. Little else was discovered except arterial hypertension. A diagnosis of softening in the left temporal lobe was made. After a month the hallucinations disappeared, and the hemiachromatopsia diminished.

Hallucinations associated with hemiachromatopsia are rare. Complex hallucinations of living objects result especially from lesions of the temporal lobe. The authors emphasize the following facts: (1) the hallucinations were in the hemiachromatopsic fields, were produced by movements of the eyes and disappeared on closing the eyes; (2) they were of short duration and consisted of images of animals or, once, of the image of dishes on the dining table; (3) they were produced during a period in which the patient was affected by heavy sleep, without oneirism. The influence of the hemiachromatopsia on the production of the hallucinations cannot be neglected. When a retinal image passes from the normal to the diseased side of the field, it becomes a new object; the perception of this difference leads the superior centers into a false pathway of identification, and a visual hallucination of short duration occurs. In the episode of seeing the table set with covers the patient noticed that the color of the table was not normal and associated with this impression a reminiscence: the table garnished. Thus, a new type of functioning, created by the hemiachromatopsia at the level of the visual pathways, occurs. A sensorial hallucination is only a visual evocation, inadequate to reality. DENNIS, San Diego, Calif.

SENILE VISUAL HALLUCINOSIS OF THE TYPE OF BONNET. P. PESME, Rev. d'oto-neuro-opht. **17**:280 (April) 1939.

Pesme describes a case of visual hallucinosis in a woman aged 93 who was practically blind from bilateral cataract, and discusses the influence of visual lesions in the production of hallucinosis. He assumes that in hallucinosis there is loss of function of the peripheral neuron with release of the cortical centers, which then function automatically and draw into action associated or neighboring cortical centers. In support of this assumption is the fact that diminution of vision from any peripheral cause favors enormously the occurrence of the hallucinatory crisis. In addition to this negative role, deformation of visual images by corneal or lenticular disorders may cause visual hallucinosis. Pesme does not believe that alcoholic retrobulbar optic neuritis can produce positive scotomas,

although the latter may play a part in the mechanism of visual hallucinations. Hallucinations can evolve only on a terrain made ready by a functional cerebral disturbance due to a local disorder, or to a general disorder with cerebral repercussions. In Pesme's patient the quality of the hallucinations varied with the state of health; in her last illness the hallucinations became a veritable crisis of oneiric delirium.

DENNIS, San Diego, Calif.

VISUAL HALLUCINATIONS IN THE BLIND. G. WEILL, Rev. d'oto-neuro-opht. **17**: 294 (April) 1939.

Weill finds that in general totally blind persons do not complain of visual hallucinations. He describes 2 cases of blindness with colored visions, in 1 of which the patient was tormented to such a degree that serious nervous disturbances developed. It is possible that many blind persons have visual hallucinations, but they remain undiscovered because the victims are not disturbed by them. The hallucinations become an obession only under the influence of some psychic factor. They must be considered psychic phenomena, the point of departure being the local and organic lesion.

DENNIS, San Diego, Calif.

VISUAL HALLUCINATIONS AND INFUNDIBULOTUBERIAN DISTURBANCES OF THE MENOPAUSE. J. A. BARRÉ and HELLE, Rev. d'oto-neuro-opht. **17**:296 (April) 1939.

It is possible that irritation from the peduncular region may be transmitted directly or indirectly to different cortical areas, and that it is in these areas that visual hallucinations are formed. Barré and Helle report the case of a woman aged 51 who one year previously had begun to gain weight and to exhibit unpleasant changes of character. The menopause was in progress. Later there developed somnolence, excessive thirst and visual hallucinations (a black man appeared in her bedroom and refused to leave; muffled footsteps of persons, not always seen, were heard). Examination gave essentially normal results. After the menopause the patient was much improved, but she still had crises of nervousness and emotional excitation with insomnia. The "black man" still appeared at times, but his appearance was changed and he spoke to her in a foreign tongue. The hypersensitivity, emotional disturbances and changes of character and judgment suggest that the cortical receptor of visual impressions, and perhaps the prefrontal area, play a relatively more important part in the genesis of visual hallucinations than the peduncular region, which is an elementary basis of such experiences.

DENNIS, San Diego, Calif.

OLFACTORY HALLUCINATIONS AND CEREBRAL TUMORS. J. A. BARRÉ and SCICLOUNOFF, Rev. d'oto-neuro-opht. **17**:298 (April) 1939.

Barré and Sciclounoff report a case of olfactory hallucinations with uncinate crises in a man aged 36. The presence of slight stasis, headaches, a unilateral pyramidal deficit and lateropulsion with rotation around the vertical axis permitted an early diagnosis of tumor of the hippocampal region, which was later verified. Olfactory hallucinations have great localizing value, provided there is no damage of the olfactory nerve endings. The mechanism of these hallucinations is not yet established.

DENNIS, San Diego, Calif.

LABYRINTHINE DISTURBANCES WITH PAPILLARY EDEMA IN THE COURSE OF MYELOID LEUKEMIA. R. MAYOUX, Rev. d'oto-neuro-opht. **17**:346 (May) 1939.

Mayoux reports the case of a woman aged 32 who had typical myeloid leukemia; the blood contained 320,000 leukocytes per cubic millimeter, of which 44 per cent were polymorphonuclears and 14 per cent myelocytes. Deafness, ver-

tigo and papillary stasis developed rapidly. There was spontaneous horizontal nystagmus to the left and no reaction to the caloric test. Two types of labyrinthine lesions are observed in the course of myeloid leukemia: hemorrhage in the labyrinth and myeloid infiltration. It may be assumed that the same type of edema existed in the labyrinth as in the eyegrounds. Myeloid infiltrations are abundant around blood vessels; often they invade the vascular lumen, causing thrombosis.

DENNIS, San Diego, Calif.

SUDDEN AMAUROSIS FIFTEEN DAYS AFTER CRANIAL TRAUMATISM. BEAUVIEUX, POUYANNE, BESSIÈRE and BERGOUIGNAN, Rev. d'oto-neuro-opht. **17**:422 (June) 1939.

The authors report the case of a youth aged 19 who, fifteen days after a traumatic meningeal hemorrhage, became completely blind in both eyes. There developed also peripheral paralysis on the left side, diplopia, somnolence, headache and abolition of the tendon reflexes of the limbs. Ophthalmologic examination revealed loss of the pupillary light reflex, bilateral papillary edema and dilatation of the retinal veins. After the intravenous use of a hypertonic solution of dextrose vision improved, but the stasis was replaced by atrophy. The amaurosis was undoubtedly related to the traumatism, but its late appearance is difficult to explain. The influence of an intercurrent, short-lived furuncle of the left orbital arch was negligible. The possibility of the sudden blocking of the sylvian aqueduct was eliminated. Optochiasmatic arachnoiditis of an abnormal form is suggested, although the evolution of this disease is usually less acute, papillary stasis is rare and alteration of the visual fields is characteristic.

DENNIS, San Diego, Calif.

EXTRAOCULAR MOVEMENTS AND THEIR ABNORMALITIES. A. KESTENBAUM, Confinia neurol. **2**:121, 1939.

Kestenbaum distinguishes five cardinal types of associated ocular movements, basing his classification on clinical findings and on ontogenetic development. Three of these are rapid movements: voluntary directional movements, optically elicited attraction movements and attraction movements secondary to other types of sensory stimuli; two are slow movements: compensatory following movements and countermovements of vestibular origin. Complex ocular movements can be reduced to these five fundamental types. Compensatory movements on passive rotation of the head, for instance, may be considered to be a combination of compensatory following movements and vestibular countermovements. The quick phase of opticokinetic and of vestibular nystagmus is a directional movement plus an optically elicited attraction movement. According to Kestenbaum there are four types of disturbance of gaze, which he classifies as follows: (1) loss of all movements; (2) retention of vestibular countermovements; (3) retention of vestibular and following movements, and (4) retention of all movements except directional movements.

DE JONG, Ann Arbor, Mich.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

GILBERT HORRAX, M.D., *in the Chair*

Regular Meeting, May 18, 1939

ACTION POTENTIALS OF MUSCLES IN "SPASTIC" CONDITIONS. DRS. PAUL F. A. HOEFER and TRACY J. PUTNAM.

This article appears in this issue of the ARCHIVES, page 1.

PARALYSIS AGITANS AND ATHETOSIS: MANIFESTATIONS AND METHODS OF TREATMENT. DR. TRACY J. PUTNAM.

I shall show two moving pictures. One presents data gathered during the last seven years in regard to athetosis: the history of the disease, clinical types, electromyographic studies, presentation of pathologic material and explanatory diagrams. The results of treatment by reeducation and by curare are shown. Examples of treatment by cortical excision, section of anterior roots and section of extrapyramidal tracts are presented.

The other picture is devoted chiefly to the surgical treatment of unilateral paralysis agitans, although other aspects of the disease and its treatment are briefly touched on. The results of cortical extirpation in 1 case and of complete section of the lateral pyramidal tract in 3 cases are shown.

The 2 cases of cortical resection were contributed by Dr. Paul Bucy.

The chordotomies were performed at the Neurological Unit of the Boston City Hospital, with few exceptions. Forty-three operations of this type have been performed on 36 patients with athetosis. There have been 4 postoperative deaths, 1 among the last 25 patients, two weeks after the operation, from pneumonia. Some degree of improvement, slight or considerable, has been obtained in the majority of the surviving patients; in 26 cases it was believed to have justified the operation. The degree of improvement has been higher in recent cases.

Complete section of one lateral pyramidal tract for paralysis agitans has been performed in 3 cases. Substantial relief has been obtained in all, with less disability than results from removal of the motor cortex. Partial section of the pyramidal tract has given some relief in 2 cases, none in a third. The operation has been well borne, even by patients in poor condition.

DISCUSSION

DR. T. J. C. VON STORCH: Has Dr. Putnam seen much autonomic change after section of the anterior column?

DR. SAMUEL EPSTEIN: Will Dr. Putnam make some comment about the operation on the cerebral cortex as advocated by Dr. R. M. Klemme, of St. Louis?

DR. STANLEY COBB: I rise with mixed emotions for the discussion of this paper. There is an emotion of admiration because Dr. Putnam is to become the head of the largest neurologic hospital in the United States. There is sorrow at the thought of parting from Tracy Putnam. And there is chagrin at the idea of losing a man so important to our community and school.

For a long while I have had special interest in the etiology and physiology of rhythmic tremors. There is one aspect which I should like to ask about; perhaps the best way is to make an outline on the blackboard. The diagram shows the different anatomic connections of the midbrain, diencephalon and cerebrum. The

evidence presented makes me believe that interruption of the sensorimotor mechanism at various points may result in tremor; a lesion of any one nucleus does not explain all the clinical phenomena. By the same reasoning, operative lesions at various levels might stop tremor. Has any one yet tried thermocoagulation of the outer layers only of cortical area 6?

DR. TRACY J. PUTNAM: In reply to Dr. von Storch: Foerster pointed out that the ordinary chordotomy for pain produced lowering of the blood pressure and vasodilatation and decreased sweating on the side of operation. He used it in 1 case for the relief of hypertension. The results are more striking after section of the anterior column. Sweating is abolished. Vascular constriction is decreased for months at least. The subject is now being studied by Dr. Stanley Novak and his associates.

In reply to Dr. Epstein: I saw a moving picture of Dr. Klemme's patients. Most of his patients appear to suffer from paralysis agitans rather than from athetosis. The operation aims at removal of the premotor cortex. He has obtained some excellent clinical results.

This may serve as an introduction to what I should like to say in reply to Dr. Cobb's remarks. There is still ignorance of the details of organization of the pyramidal system, and the extrapyramidal system appears so much more complicated that the human mind can grasp it only by means of schemata which are necessarily inadequate. A further difficulty is that the same procedure appears to produce varying results in different hands; witness the conflict over the therapeutic value of cortical extirpations for athetosis. This is doubtless in part because the extent of the operation is difficult to judge. In a recent case of unilateral athetosis, the result of chordotomy was so disappointing that reoperation was decided on. A slightly more radical operation produced a thoroughly satisfactory result. A further hazard is the difficulty of evaluating the operative results. Patients are often disappointed if they fail to regain complete normal activity, even though a substantial improvement is obtained. It seems to me that one is still in the stage of gathering empiric facts and that interpretation will have to wait. At least, attempts at surgical treatment of the dyskinesias have provided more data concerning their physiology than were possessed before.

PHILADELPHIA PSYCHIATRIC SOCIETY

BALDWIN L. KEYES, M.D., *President, in the Chair*

Regular Meeting, April 21, 1939

TRANSVESTITISM AND OTHER CROSS SEX MANIFESTATIONS. DR. NATHANIEL S. YAWGER.

Transvestitism, or cross dressing, is the strange adoption of a few men and women, and certain historic personages have had recourse to such modes of dress. Dr. Mary Walker, who was the daughter of a physician, after the age of 29 appeared continuously in some form of male attire. She was an assistant surgeon in the Civil War and was equipped with the uniform of male officers. Havelock Ellis wrote extensively of the anomaly transvestitism, describing it under the title "eonism," named after a French nobleman, d'Eon, who was distinguished as a diplomat, writer and musician and was the greatest swordsman of his day. For more than thirty-five years he wore women's dresses, and not until after his death was it known that he was a man. One of my cases is that of a man who in childhood became fascinated by pictures of veiled harem women, told of in the "Arabian Nights." Subsequently, he found that he obtained sexual gratification through the wearing of a veil; this became a fetish, led to the embezzlement of

$23,000 and was followed by internment in a penitentiary. Another patient showed endocrine imbalance; this subject believed himself "half man and half woman"; he was disturbed every four weeks by what he considered to be incomplete menstruation. Thinking he might be relieved by castration, he made two attempts on himself, but pain and hemorrhage caused him to leave the work uncompleted. Sometime after, thinking he might improve his technic by practicing on another, he chose for that purpose a hobo. It was his intention just to "knock out" his man, but he hit him over the head with an iron bar so hard that he died almost immediately.

Formerly a party known as a "drag" had to be conducted with great secrecy, but in the present day wide open era admission is not difficult and audiences sometimes number thousands. The competing actors, so-called girls, come from all classes of society and may be Negro, sepia-skinned or white males. Fantastically garbed, with cupid-bow lips, plucked eyebrows and curved eyelashes, they cavort, gyrate about and flirt, enticing dancing partners from the men of various classes and colors in their audience. Police and detectives must be present to prevent intoxication, fighting and the graver degenerate tendencies. In his book entitled "Men Like Women," Berg said: "These were men who felt like women and were not ashamed of it." Tenebaum wrote of periods in history in which this state has been embraced and in which, among other characteristics, has been sex reversal of erotic roles. He spoke of the present period as one in which women display "narrow hips and bobbed hair, who smoke and swear." The Renaissance age was another, and it is said that such periods usually coincide with increase of homosexuality, transvestitism, androgynism and gynandrism. However, these deviations come within normal range and are only transitory. Freud has not revealed himself definitely on the subject of transvestitism. However, certain of his followers with variant psychoanalytic theories have presented their views: London expressed the belief that punishing a child by making it wear the clothes of the opposite sex may be the cause of transvestitism; he called this sex perversion a neurosis and regarded it as curable. Stekel's reliance was chiefly on interpretation, including active intervention in the subject's life, rather than on uncontrolled association. Stekel considered transvestitism as latent homosexuality, and even the so-called sexually normal persons as sexual inverts. Havelock Ellis differed from this view and adhered to Hirschfeld's classificatoin of homosexual, bisexual, narcissistic and asexual types. In plant life hermaphroditism is fairly common. Through the amount of exposure to sunlight and the chemical composition of the soil in which plants are grown, naturalists can, to some extent, control sex. In animals the sex attractions and desires may be changed by reversal of the sex organs. Even the more highly complex human organism may be influenced through surgical procedures and the use of hormones, so that minor physical and mental reversals are sometimes brought about.

DISCUSSION

DR. ROBERT A. MATTHEWS: About a year ago a man applied to the Philadelphia Marriage Counsel for advice; since he was unable to state clearly the advice that he needed, or was unwilling to do so, and appeared to be unusual in his attitude, it was suggested that he consult me, which he subsequently did. He was about 50 and was effeminate in attitude and appearance. He entered the office in a coy, gingerly fashion and immediately inquired if I was a scientist, which I modestly admitted I thought I was. Then he said he had a series of questions he would like to ask, the first being: "Can a man be turned into a woman?" He said he wanted to be transferred into a woman and was seeking some one who could help him bring this change about. I assured him that such a procedure was not easy and probably could not be done, whereon he brought out several newspaper clippings reporting the case of a person who had had such an operation performed, supposedly with change in sex. He then told me an interesting story. He had lived alone in a small house in a suburban community

for years, had done his own cooking and housework and attended to a little garden. He had never held a job, having a small income from an investment. His greatest pleasure was to go into the city to shop for women's clothing, which he frequently did; he had accumulated quite a feminine wardrobe. Several times a week, and sometimes daily, he donned this apparel and admired himself in the mirror. He was an amateur photographer and had taken hundreds of pictures of himself dressed in women's clothes. What had motivated his coming for help was that there were several young girls in the neighborhood, not too moral, who, he claimed, were "trying to make him," and he was afraid he might be seduced. He went away somewhat disappointed, and I have not seen him since.

DR. NATHANIEL S. YAWGER: I can say only that the case Dr. Matthews has related is one of transvestitism. These homosexual persons are not inclined to go to physicians for treatment and advice. They shun it. I have seen a few in the Eastern Penitentiary, and I find that they do not consider themselves diseased in any respect. They believe their condition is natural and that they should be allowed to follow their own inclinations.

PSYCHONEUROSES IN A HOSPITAL FOR MENTAL DISEASE: A STATISTICAL STUDY OF ONE HUNDRED MEN AND ONE HUNDRED WOMEN. DRS. CLIFFORD B. FARR and GENEVIEVE M. STEWART.

Two hundred unselected cases of psychoneuroses from the department for mental and nervous diseases of the Pennsylvania Hospital, equally divided between the sexes, but otherwise chosen in order of the patient's admission, have been analyzed and the follow-up findings after one to sixteen years recorded in 174. In 26 cases there was no record subsequent to the discharge of the patient. Psychoneurotic patients constituted from 3 to 7 per cent of the total number admitted, in recent years tending to reach the higher figure. With few exceptions, these patients represented "voluntary" admissions.

1. In this series it is difficult, if not impossible, to anticipate the type or intensity of attack from a study of the preneurotic personality.

2. While typical neurotic personalities, as described by Horney, were common in our series, nevertheless clearcut attacks did develop in seemingly competent, well integrated persons. However, these patients tended to regain their equilibrium after a comparatively short hospital residence.

3. While it seems that more women became psychoneurotic, the rate of recovery of those who were previously well adjusted was twice as great as that of men, but relapses were more frequent.

4. Patients were reported by competent psychiatrists as being psychoneurotic even if, with reservations, they became psychotic in a considerable proportion of cases as determined by subsequent admissions or reports from physicians or other hospitals. Of our 200 patients, of whom 174 were followed for from one to sixteen years, psychoses occurred in 13 per cent; in a further 18 per cent symptoms suggestive of something more than neurosis manifested themselves at times, but were not adjudged sufficient to alter the diagnosis. The incidence of psychoses in cases in which the condition was diagnosed as hysteria was 17 per cent, as psychasthenia 19 per cent, as neurasthenia 12 per cent, as reactive depression zero, as anxiety states 8 per cent.

5. Some authorities still insist that neurotic persons never commit suicide. Our series affords strong evidence to the contrary. Seven per cent of our 200 patients committed suicide early or late in the course of the illness, and, strangely, none of these were in the group which had become definitely psychotic. The incidence of suicide was slight (from 2 to 3.5 per cent) for the usual categories of hysteria, psychasthenia and neurasthenia, and high for reactive depression and anxiety states, 11.5 and 29 per cent, respectively. In an additional 18 per cent suicidal

attempts or ideas were noted. The high incidence of suicide and the low incidence of psychosis in cases of reactive depression and anxiety states may argue for their inclusion in the definitely psychotic categories.

DISCUSSION

DR. J. C. YASKIN: I am sure this paper is only a summary, and that the material will be the subject of a future presentation. I do not know whether I secured a clear picture from the presentation; so shall restate it in my own way. The authors have studied 200 patients with diagnoses of psychoneuroses who, through voluntary admission or commitment, were patients in hospitals for mental disease. The form of hospitalization required by these patients takes the group out of the large group of persons with psychoneuroses whom one is accustomed to treat in office practice. However, I am sure that the staff at the Pennsylvania Hospital could not have been wrong in making the diagnosis of a psychoneurosis, and that at the time of the classification the patients were not psychotic. Here, of course, one comes to the vital question, which I hope the authors will make clear, namely, what they mean by a psychoneurosis. They have said they considered the cases under the headings of neurasthenia, hysteria and so forth, and that later the diagnoses of reactive depressions and miscellaneous anxiety states were adopted. Anxiety state is not a sharply demarcating diagnosis. I assume that under neurasthenia were included many cases classed as anxiety states later; is that correct?

DR. GENEVIEVE M. STEWART: Yes.

DR. J. C. YASKIN: When this group of patients is compared with that encountered in office practice, one is surprised by the similarity of the two groups. There are perhaps not as many with anxiety hysterias as one observes in office practice. There is perhaps a greater number with the psychasthenic type of reaction than in the office group, but on the whole the types are essentially the same.

The next interesting point stressed by Drs. Farr and Stewart is that some of the patients did not show evidences of neurotic traits in the preneurotic state. This was my experience in an analysis of 100 cases (The Psychoneuroses and Neuroses: A Review of 100 Cases, with Special Reference to Treatment and End Results, *Am. J. Psychiat.* **93**:107 [July] 1936). I suspect that in some cases the lack of a preneurotic personality depended largely on the fact that I did not go far enough into the previous history, for had I subjected the patients to a thorough analysis of the situation I should have found neurotic traits.

I am not surprised that many of the patients showed a psychosis later, and I should not be certain that the psychoses were necessarily related etiologically to the psychoneurotic manifestations of earlier life. To state that a psychoneurosis in a person who had a psychosis years later was originally misdiagnosed is, I think, wrong. If a neurotic person lives long enough he will have diabetes, carcinoma or perhaps a psychosis. However, there are many psychoses which start with masking neurotic symptoms. This is true of the psychasthenic types of reaction, and especially of some of the severe anxiety hysterias.

I was much interested in the statement that one can hardly judge the severity of the symptoms during the neurosis by the preneurotic personality, and I think it should be so. If one sticks to the definition that the neurotic personality is one in which the neurotic symptoms are built into the character, then, depending on the severity of the precipitating cause, the symptoms may be severe or mild. On the other hand, the prognosis can be formulated by an intensive study of the preneurotic personality traits. Thus, the finding of compulsive-obsessive tendencies indicates a deep-seated psychologic distortion and should make the prognosis less favorable.

I am not surprised at the frequency of suicidal ideas and tendencies and their actual occurrence in this group. Suicide is an end result of personality distortion

plus exciting factors. Suicide, therefore, occurs in patients with psychoses and psychoneuroses and in the so-called normal person, who may often have suicidal ideas and tendencies and may even destroy himself before showing clinical symptoms of a disease entity.

DR. CLIFFORD B. FARR: The question of the distribution of these cases within the psychoneurotic group has been raised. That is somewhat artificial; so to avoid confusion, we have adhered, with the exceptions noted, to the official diagnoses as reported to the State Bureau of Mental Research. Dr. Stewart and I frequently did not agree with one another or with the original diagnoses, though the latter were made by men whom we regarded as outstanding psychiatrists. Patients present different symptoms at different times, and physicians, in turn, stress different congeries. The condition of a patient studied successively in four well known private hospitals was classified differently in each, though as psychoneurotic in all. Dr. Yaskin wrote a paper in which he described cases to illustrate anxiety in patients from all these groups. We, on the other hand, have resorted to the diagnosis of anxiety state only in cases in which the symptoms were so dominant that we could not escape it.

NEUROPSYCHIATRIC DISORDERS OCCURRING IN CUSHING'S SYNDROME: PITUITARY BASOPHILISM. DR. NATHAN S. SCHLEZINGER, New York.

Recently, Maclay and Stokes have reported a case of Cushing's syndrome in which a psychosis developed. I shall describe a case in which the development of a similar psychosis was an outstanding feature. This patient also showed evidence of an extrapyramidal neurologic disorder which, so far as I have been able to determine, has hitherto not been described in a case of Cushing's syndrome.

REPORT OF A CASE

L. F. G., a woman aged 27, was admitted to the New York State Psychiatric Institute and Hospital in September 1936, with a history of major tics since early childhood. Early in 1934 there gradually developed change in body contour; in September 1934 there was a sudden onset of a psychosis characterized by marked depression and self-condemnatory ideas and associated with amenorrhea. There were persistence and progression of all symptoms. On admission the patient showed physical signs characteristic of Cushing's syndrome, plus evidence of extrapyramidal disease of the central nervous system; the mental picture was chiefly that of depression and psychomotor retardation. The condition remained unchanged until her death in February 1937, following left adrenalectomy.

Postmortem examination showed: external appearance characteristic of Cushing's syndrome; a small, atrophic right adrenal gland; histologically benign neoplasm of the left adrenal gland; marked hyaline changes (Crooke) in the basophilic cells of the adenohypophysis; marked congestion and edema of the parenchyma of the brain, with focal areas of encephalomalacia in the frontal lobes.

There existed in this patient a depressive psychosis and an extrapyramidal neurologic disorder, the overt development of both being associated temporally with that of the specific endocrine disorder. It is suggested that the etiologic factor in the complex clinical picture observed in this case may be a neuroendocrine or an encephalitic disorder.

Review of the literature reveals that mental symptoms not infrequently occur in Cushing's syndrome and that mental depression of varying degree has been a prominent feature in these psychiatric disorders. The mental symptoms may be a direct manifestation of the underlying specific endocrinopathy, although the mechanism of their production remains obscure. It is possible that the form of psychiatric disorder, namely, depression, in these cases bears a close relationship to manic-depressive and involutional psychoses.

DISCUSSION

DR. ROBERT A. MATTHEWS: Dr. Schlezinger has pointed out a number of possibilities which should give food for thought. I cannot say that I am altogether in accord with him in certain of his interpretations, but that does not mean, of course, that they are not correct. The question of the incidence of depression in cases of Cushing's syndrome suggested reading what Cushing himself found in the 16 cases that he reported (Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932). They were not all his own cases, so he did not actually observe every case himself. However, it is interesting to note that in only 3 of this group were mental symptoms noted, and in no case were they stressed. In 1 instance (case 8) it was noted that the patient had occasional headaches, with impairment of memory. In case 9 the patient was made sleepless by trembling of the body, noises in the ears, dreams and visions. In case 11 the patient could not concentrate and had fits of unnatural irritability, alternating with periods of depression. In the other cases no noteworthy mental symptoms were mentioned. It seems that such a keen observer as Cushing would have stressed mental symptoms had they been outstanding, although, considering the psychologic aspects of the disease, mental disturbances should frequently develop.

In the case Dr. Schlezinger described, I was impressed by the past history: The patient had shown certain neurotic tendencies since birth. She had ticlike movements, enuresis and great sensitivity in regard to her body, and had had an operation performed on her nose to correct its appearance, which was followed by emotional disturbance. Her tendency to answer questions by saying "I don't know" indicates a kind of withdrawal, and there was mention of her childish behavior on a number of occasions. An interesting point is that after operation, which was apparently a great shock, her speech returned to normal for a few hours and she was able to talk in a normal voice. Unfortunately, Dr. Schlezinger's reports on the neuropathologic changes in the basal ganglia were not complete; those reported did not definitely confirm the diagnosis of encephalitis; there was change in the ganglion cells, but the lesions were not as marked as one would usually expect.

DR. ELI MARCOVITZ: I wish to ask Dr. Schlezinger about the softening of the frontal lobe. Was that due to a terminal condition, or was it the result of the illness?

DR. NATHAN S. SCHLEZINGER: The focal areas of encephalomalacia in the frontal lobes were of recent origin, as proved by microscopic study, and did not exist during the course of the patient's illness.

In regard to the pathologic changes in Cushing's syndrome: It is not possible in this case definitely to answer that question. I doubt whether it will be settled in the near future. It is difficult at present to associate the features of Cushing's syndrome with any single lesion of the endocrine glands. When an adrenal tumor is present, the question arises whether the cellular changes in the hypophysis may produce a secondary change in the adrenal gland.

In regard to the presence of primary endocrine involvement: I believe that the evidence indicates that the channel of effect runs from the nervous system to the hypophysis rather than in the reverse direction.

POSTOPERATIVE DYSERGASIA. DR. WILLIAM FURST (by invitation).

The term dysergasia was first proposed by Adolph Meyer to designate disorders of mental function due to permanent or transient changes in the brain, possibly related to disturbances of nutrition and/or circulatory support of the cerebral structures. This concept of dysergasia as a disturbance of the internal environment as a whole, and not of the brain itself, seems necessary for adequate understanding and treatment of such vague conditions as "toxic psychosis," "toxic delirium," "psychosis associated with somatic diseases" and "exhaustion delirium."

Ten cases selected from the records of the Philadelphia General Hospital, during a ten year period, in which a postoperative psychotic response occurred were analyzed from the dysergastic point of view. A psychotic episode occurring three days after appendectomy was described in detail in a case in which a diagnosis of toxic psychosis due to alcohol was made but in which increasing sedation and use of whisky sufficed only to increase the psychotic manifestations. In this case prolonged hypotension during operation in a hypertensive patient, dehydration with excessive sedation, albuminuria, decreased alkali reserve, hypochloremia, impairment of liver function and transient azotemia may have been related factors in producing the psychosis. Limitation of sedatives and increase in the fluid intake probably corrected most of these factors and resulted in disappearance of the mental disturbance.

From a review of the literature, it becomes evident that even with due regard to psychopathologic factors affecting production of the postoperative psychosis, there may be etiologic factors which may best be comprehended by the concept of dysergasia. Reinhold emphasized the relationship of dehydration, anoxia, transudation of plasma proteins and lipoids on cellular permeability and neural integration. Courville stressed the occasional mental and emotional manifestations following anesthesia induced with nitrogen monoxide. Coma, delirium and/or mania, hysterical outbursts and transient hallucinatory states have resulted. Boyce and McFettridge demonstrated that liver function, as measured by hippuric acid excretion (Quick test), showed a decrease of 25 per cent after ether anesthesia, which they attributed to thermal loss at operation with decreased hepatic efficiency, loss of liver glycogen or anoxemia. After spinal anesthesia, liver function decreased 49 per cent. This might be explained by the fall in blood pressure, with decreased oxygen supply to the liver, or elimination of the spinal anesthetic by way of the liver, producing depression of function. Dextrose given before and after operation protects against this hepatic dysfunction. In the light of this work, Lewy's studies on the relationship of vitamin B deficiency to diseases of the liver and the secondary effect on neural function take on increasing importance.

The hereditary background; the preoperative mental state, and environmental, constitutional, nutritional, metabolic, vascular, endocrine and infectious factors, with excessive sedation, are intimately related in the comprehension of the diagnosis and treatment of the postoperative psychosis. Adequate laboratory study frequently indicates the organ systems responsible for the disturbance of the internal environment. Incorrect diagnosis and treatment prolong convalescence. Further investigation in this neglected field is indicated.

DISCUSSION

DR. S. B. HADDEN: I congratulate Dr. Furst for bringing this important subject to the attention of the society. I am sure that if he had gone back another decade he would have found an even higher incidence. When spinal anesthesia was first widely used, it was not uncommon for the systolic blood pressure to drop from 230 to 100 mm. or lower.

The factor in the case Dr. Furst presented in detail is definitely in accord with the mechanism I described in which there is lowering of blood pressure, with lowering of the rate of circulation through the brain. Edema of the brain results, with anoxemia of the brain cells and oversedation. A vicious cycle is set up, since the sedatives induce added anoxemia.

The usual management of conditions of this sort is sedation. This is frequently true in the dysergastic states that occur after long-standing infections, even acute infections, such as pneumonia, in which the decrease in chlorides plays the major role. Little attention is paid to the state of circulation or the electrolytic balance of the blood. Restoration of the electrolytic balance is one of the most important features, and many more patients will respond to administration of chlorides and cardiac stimulants than will be benefited by barbiturates.

PHILADELPHIA NEUROLOGICAL SOCIETY

JOSEPH C. YASKIN, M.D., *President, in the Chair*

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INTRADURAL EXTRAMEDULLARY TUMOR (MENINGIOMA) INVOLVING THE SPINAL CORD AND EXTENDING INTO THE INTRACRANIAL CAVITY: REPORT OF TWO CASES. DR. FRANCIS C. GRANT.

Two cases are reported because of the infrequency with which tumors spring from the spinal dura and grow upward into the cranial cavity.

CASE 1.—D. T., a white woman aged 23, was admitted to the neurologic service of Dr. W. B. Cadwalader, of the Hospital of the University of Pennsylvania, on Feb. 9, 1939, with the chief complaint of weakness and spasticity of the limbs. In June 1938 the gradual onset of weakness in the right foot had been noted; it increased until the right leg became weak and incoordinate. By November 1938 the right hand had become involved, and the left leg occasionally gave away under her. In December 1938 and January 1939 the weakness in the legs and right hand increased until she could neither stand nor walk. Assistance was required before she was able to sit up. Pain had not been noted until two weeks before admission, when it appeared in the right groin. There had been no loss of sphincter control.

Neurologic Examination.—The cranial nerves were normal except for concomitant, convergent, alternating strabismus, which had been present since birth. Nystagmus was not noted. The head was carried drawn somewhat to the right, with the chin slightly depressed toward the right, but pain or limitation in the movements of the head or neck was not noted. Slight atrophy of both arms was present and was more marked on the right side, especially in the hand. The reflexes in the upper extremities were markedly hyperactive. A Hoffmann sign was present bilaterally. There were pronounced ataxia and incoordination in the movements of both arms, with bilateral astereognosis. Sense of position and passive movement was impaired. Motor loss in both upper extremities was definite, but more in the right. The abdominal reflexes were much diminished. The reflexes in the legs were hyperactive, with mild spasticity, marked clonus and a prompt Babinski reflex bilaterally. Sense of position was diminished in the toes. Vibration sense was impaired as high as the clavicle on both sides.

Sensory examination at first revealed apparently patchy, changeable hypesthesia over the trunk and legs; a more detailed study showed that normal sensation was present only over the face in the distribution of the trigeminal nerve and that a definite sensory level for touch, pain and temperature existed at the second cervical dermatome.

Comment.—The general impression was that the patient had a progressive, degenerative disease of the spinal cord. To every one's surprise, a lumbar puncture and the Queckenstedt test revealed complete block. The fluid was clear and colorless, containing only 25.2 mg. of protein per hundred cubic centimeters. Combined lumbar and cisternal puncture was carried out; when the lumbar needle again gave evidence of a complete block 1.5 cc. of iodized poppyseed oil was injected into the cistern. None of the oil passed below the level of the foramen magnum. A small defect in the outline of the oil was apparent on the left side, suggesting the presence of a tumor protruding into the cistern. Careful repetition of the sensory examination now showed that all modalities of sensation were normal only in the distribution of the trigeminal nerve and that they were definitely impaired below the second cervical dermatome on either side.

Operation.—On February 23 suboccipital craniectomy combined with laminectomy of the first, second and third cervical spines was performed. A well encapsulated tumor was observed lying on the left anterolateral aspect of the cord, curling over the rim of the foramen to extend for about 1 cm. into the cranial

cavity. The tumor extended downward to involve the fourth cervical segment and had compressed the cord to the right. Unfortunately, it was attached to the dura anterolaterally throughout its entire length, the only free portion being that which extended upward into the cranial cavity. The tumor itself was tough and avascular, but had become involved thoroughly with the spinal vessels emerging with the upper cervical nerves. The upper pole of the tumor, down to the point where it became firmly attached to the dura, was first removed and the lesion sectioned at that level. The lower portion of the growth with its dural attachment was then excised. Pathologic study showed that the tumor was a meningioma.

Course.—The patient made a satisfactory postoperative recovery. Fortunately, the maneuvers necessary to remove this large growth did not injure the cord. The spasticity in the legs decreased, and on discharge, on March 26, power was slowly returning in all extremities. The patient was seen again on May 10. At this time she could stand alone and walk with assistance. The spasticity had entirely disappeared in the legs, although the hyperactivity of the reflexes was pronounced and clonus and a Babinski sign were noted in the left leg.

CASE 2.—W. B., a white man aged 52, was admitted to the neurosurgical service of the University of Pennsylvania Hospital on Jan. 31, 1939, with the chief complaint of inability to walk. In January 1938 weakness of the left leg had been noted. By April 1938 the right leg was also weak. He complained of burning sensation in the calf of each leg. At this time, when he walked he felt that his knees would bend backward. The weakness in the legs continued until he was scarcely able to walk. By November 1938 weakness of the left arm became apparent. He was then entirely unable to walk because of weakness of the legs and dizziness. Sphincteric difficulty was never apparent. Prior to his admission to the hospital, spinal hydrodynamic studies had been made and thorium dioxide had been injected into the lumbar subarachnoid space, without a definite diagnosis being reached. After this procedure, headache developed and became pronounced.

Examination.—The patient, well oriented and conscious, was unable to sit up unassisted. The cranial nerves were normal except for papilledema, of 2 D., in each eye, slight but definite horizontal nystagmus and weakness of the spinal accessory nerve bilaterally. Marked atrophy of the left shoulder girdle was present, with questionable atrophy of the dorsum of the left hand. Fibrillary twitching of the left deltoid muscle was noted. Marked weakness of the left arm and leg was present. Reflexes were generally hyperactive, but were rather more active on the right side than on the left. A Babinski sign, without clonus, was found on the left. Marked incoordination was present in all extremities, especially on the left side, and was more pronounced with the eyes shut.

There was marked nuchal rigidity, with pain on extreme rotation. Touch and temperature sensations were normal throughout. Patchy hypalgesia for pain was present throughout the right leg anteriorly and posteriorly below Poupart's ligament. Vibration sense was absent over the trunk and extremities. Gnostic sensation and stereognosis were normal.

Lumbar puncture and a Queckenstedt test showed a complete block. A combined lumbar and cisternal puncture revealed complete block in the lumbar manometer, but a normal reaction in the needle in the cistern. Iodized poppyseed oil was injected through the cisternal needle. Roentgenographic studies showed a partial block in the region of the first cervical body, with a filling defect on the left side of the spinal canal, indicative of a lesion at this point.

Operation.—On February 10, suboccipital craniectomy and laminectomy of the first, second and third cervical vertebrae were carried out. At the level of the foramen magnum on the left lateral aspect of the spinal cord a solid, encapsulated tumor was exposed. The tumor extended upward to involve the under surface of the left cerebellar hemisphere and downward to press on the upper three cervical segments. Fortunately, the dural attachment of the tumor was not wide, and after it was sectioned complete removal of the tumor was possible. The left spinal accessory nerve was sacrificed. Pathologic examination showed the tumor to be a meningioma, with many psammoma bodies.

Course.—Postoperative convalescence was slow and tedious. Gradually, however, power returned in the trunk and extremities. The patient could walk with assistance before discharge. A recent letter, in April 1939, stated that he could get about without assistance, although he moved slowly.

COMMENT

These 2 cases present many points of interest. In each the sensory examination was of uncertain value. In case 1 the question whether any definite sensory changes existed led to the view that the condition was due to multiple sclerosis or other degenerative disease of the cord. In case 2 the lack of definite sensory findings together with nystagmus, choked disks and incoordination of the arms made the diagnosis of cerebellar tumor easily tenable. In fact, as the operative notes show, the tumor involved the under surface of the cerebellum, and its protrusion into the basilar cistern explains the papilledema. The Queckenstedt test plus injection of iodized poppyseed oil made easy the localization of both these otherwise obscure lesions.

DISCUSSION

DR. TEMPLE FAY: Did both these tumors lie posterior to the posterior roots? In other words, were the posterior roots pushed down? I had a case in which the tumor was located between the anterior and the posterior roots and removal proved difficult.

DR. FRANCIS C. GRANT: Yes, Dr. Fay. The patient in case 1 has more weakness of the spinal accessory nerve than she had before, and the anesthesia is more pronounced. I think that in removing the tumor I had to sacrifice the second and third cervical roots, since they were all matted in the tumor. I may also have had to sacrifice some of the anterior roots, but I am not sure.

HYPERTROPHY OF THE LIGAMENTA FLAVA. DR. ROBERT A. GROFF.

Three patients presented hypertrophy of the ligamenta flava between the fourth and the fifth lumbar lamina. An analysis of the history of these patients, together with that in the 27 cases reported in the literature, reveals that it is not unlike that associated with other lesions in this location. Low back pain is the predominating symptom. Irradiation of the pain to one or both legs invariably occurs, and the patient is more comfortable standing or sitting. Sexual impotence may develop. In over 50 per cent of the cases a history of trauma preceded the pain by months.

Neurologic signs are present in most patients. A diminished achilles reflex is the most constant finding. If sufficient time elapses, motor, sensory and trophic disturbances, confined to the region supplied by the lower lumbar and sacral roots, develop. An increase in the protein content of the spinal fluid usually occurs in these cases, as well as in those of other obstructive lesions of the spinal canal. Opaque oil or air injected into the dural sac demonstrates the pathologic changes.

The mechanism by which hypertrophy of the ligamenta flava is produced is explained by the observation on 1 patient. An abnormal movement between the two vertebrae where the pathologic condition existed was demonstrated at the operating table. This abnormal movement sets up the irritation which causes thickening of the ligament. For this reason, the suggestion is made that all patients with this lesion should be submitted to fusion by an osteoperiosteal graft after the ligament has been removed. It is believed that this procedure will prevent difficulties after the operation.

DISCUSSION

DR. FRANCIS C. GRANT: How much protrusion into the spinal canal was seen when the lesion was exposed? In the 1 or 2 cases I have seen I was not sure that there was hypertrophy of the ligamenta flava. I have always been skeptical about this particular lesion. I have seen 2 cases, in both of which the diagnosis was made not on anything that I described but on the pathologic change.

DR. MICHAEL SCOTT: Were Dr. Groff's patients of full stature?

DR. TEMPLE FAY: In the past, before injection of air was employed, I could not find anything to account for the symptoms, and was surprised that the patients were relieved after operation. However, injection of air shows without question that there is a defect. In 1 case there was unilateral, and in 2 bilateral, increase in the size of the ligaments.

DR. ROBERT A. GROFF: In reply to Dr. Grant: One can see the actual compression of the dural sac at operation. However, it is not nearly as marked as the air studies would make one believe. The point is that certain movements of the spine allow compression of the dural sac and that other movements release it. In the second case which I reported I was not sure there was constriction. However, in repeating the observation on fluoroscopic examination I saw a marked constriction opposite the fourth lumbar interspace. There was lateral extension of the ligament, and that was partly the cause of the symptoms of root involvement.

In answer to Dr. Scott: The 3 patients were all short. However, orthopedists say persons with this lesion have lost the curve of the back and that that is characteristic.

The first patient, a man, had paralysis of the sphincters. He had the most marked hypertrophy that I have seen. When the dural sac was opened adhesions matting the nerve roots in that vicinity were seen. However, the adhesions could be separated, and there was a free flow of spinal fluid from the level of the lesion.

TRIGEMINOAURICULAR REFLEX. DR. MICHAEL SCOTT.

The following case is presented for an opinion as to whether the condition is a reflex, and, if so, as to what neural pathway it follows.

REPORT OF A CASE

G. D., a man aged 22, was admitted to the Temple University Hospital, to the service of Dr. Temple Fay, on Nov. 5, 1938, with a history of pain over the left eye and temporal region and loss of weight and strength for six months before admission. One and a half months before admission there had been the onset of jargonaphasia, diplopia and vomiting. The past history was without significance, except for an occasional generalized convulsion about four years previous to admission. There had been no definite history of injury to the head.

Neurologic Examination.—The patient was alert and cooperative. There was slight hesitancy in speech, but no obvious anomia or jargonaphasia. The right pupil measured 6 mm.; the left, 4 mm. Both reacted well to light and in accommodation. The left palpebral fissure was narrower than the right. The eyegrounds showed bilateral choking of 4 to 5 D. The visual fields were grossly normal. There was tenderness of the left side of the head on percussion. There was weakness of the lower two thirds of the right side of the face, as well as slight weakness of the right arm and leg and a Babinski sign. Roentgenograms showed erosion of the sella turcica and calcification in the left frontotemporal area. Dr. Fay performed an exploratory craniotomy and removed a large clot (subcortical) below the inferior frontal and anterior superior temporal convolutions on the left side. The incision healed well until the eighth postoperative day, when the anterior limb of the wound opened slightly because of extrusion of a deep silk suture. Three days later, while the incision was being dressed, the following reflex was noted: When the left eyebrow was gently but firmly stroked toward the lateral canthus, the left auricle pulled upward and backward. This movement could be produced at will by pressing directly into the lateral canthus against the bony margin of the orbit. It was impossible to produce this reflex on the opposite side. Pulling on the eyebrows did not produce it. Stimulation of the nasal mucosa was likewise unproductive. During the reflex movement there was no raising or wrinkling of the frontalis muscle. The movement was not voluntary, and the patient insisted that he had never voluntarily made the movement nor had any one noticed it before. The reflex persisted and was active at the time of discharge, when the incision had healed completely.

Comment.—I am at a loss to describe the origin of the reflex. Many patients having a similar type of incision and location of lesion have been tested, but the reflex could not be elicited. For want of a better term, it has been called the trigeminoauricular reflex, the afferent pathway probably being the fifth nerve and the efferent pathway the seventh.

A moving picture of the reflex was shown.

DISCUSSION

DR. B. L. KEYES: Did this patient have voluntary control of the movements of his ears? Could he wiggle one ear and then the other if he wished? He was sensitive on this side, and had an almost voluntary movement in response to this irritation.

DR. E. A. SPIEGEL: This is an old reflex, for it is well known that one can produce movement of the ears. I remember that about fifty years ago, in Vienna, a man was shown before a society who was able to move his ears.

DR. MICHAEL SCOTT: The thought expressed by Dr. Keyes had occurred to me, and I suggested it as a possibility. I tried to have the man wiggle his ears, and he could not do it. There was no voluntary ability to wiggle the ears, either on one side or the other. I discovered a statement in the literature to the effect that stimulation of the central ends of the sympathetic fibers can produce backward moving of the ear, but I do not understand the mechanism.

DIABETES INSIPIDUS, WITH RESULTS OF OPERATION: REPORT OF A CASE. DR. MICHAEL SCOTT.

A. C., a man aged 30, referred by Dr. Solomon Solis-Cohen, was admitted to the neurologic-neurosurgical service of Dr. Temple Fay on Nov. 18, 1938, with the complaint of diabetes insipidus for three years and occipital headache for three months. Urination was partially controlled by solution of posterior pituitary U. S. P. given intranasally. In addition, the patient had attacks of sweating and weakness, which were often relieved by candy. He had hot flashes, loss of libido, loss of weight and strength, lack of beard, difficulty in acquiring tan in the summertime and, at times, confusion.

Neurologic Examination.—The results were normal except for the following ocular signs: There was concomitant, divergent strabismus; the right pupil was slightly larger than the left; both reacted only slightly to light but well in accommodation (Argyll Robertson pupil).

The specific gravity of the urine ranged from 1.006 to 1.010. The blood counts and blood chemical constituents were within normal limits. The Wassermann reaction of the blood was negative. The basal metabolic rate was minus 36 per cent, and the blood cholesterol, 354 mg. per hundred cubic centimeters. The dextrose tolerance curve was flat, with a fasting value of 82 mg. per hundred cubic centimeters, a peak of 131 mg. at one hour, 67 mg. at four hours and 93 mg. at six hours.

On admission the patient was using a few cubic centimeters of solution of posterior pituitary intranasally every four to six hours. His fluid intake averaged 75 ounces (2,126 cc.) per twenty-four hours and his output 70 to 90 ounces (1,984 to 2,551 cc.). The blood pressure was about 110 systolic and 70 to 80 diastolic. The pulse rate was 80; the respiratory rate 20. The temperature varied from 97 to 98 F. by mouth. The weight at admission was 154 pounds (69.9 Kg.).

A roentgenogram of the skull showed erosion of the sella turcica, and the pineal gland was displaced upward and backward.

Course.—Administration of solution of posterior pituitary was stopped for three days, and the fluid intake rose to 170 ounces (4,820 cc.) and the output to 220 ounces (6,237 cc.) per twenty-four hours. The patient lost 8 pounds (3.6 Kg.) in three days, the weight dropping from 152 to 144 pounds (68.9 to 65.3 Kg.).

Encephalographic examination was made on December 5. The initial pressure was 12 mm. of mercury. One hundred and fifteen cubic centimeters of fluid was removed and 90 cc. air injected. The injected air filled the fourth ventricle, but was stopped at the aqueduct of Sylvius. This finding, together with the erosion of the clinoid processes and the posterior and upward displacement of the pineal gland, suggested a tumor or inflammatory lesion with a block and dilatation of the third ventricle. The Wassermann reaction of the spinal fluid and the colloidal gold curve were normal; the protein content was slightly increased; the sugar measured 62 mg. and the chlorides 814 mg. per hundred cubic centimeters; there were 48 white cells (26 per cent polymorphonuclears and 74 per cent lymphocytes). After the encephalographic procedure the use of pitocin as a nasal spray was started, the patient using a few cubic centimeters every four hours. The fluid intake for twenty-four hours averaged 40 ounces (1,134 cc.) and the output 55 ounces (1,559 cc.), for a period of seven days. On December 7 the chloride excretion in the urine was 57 mg. per hundred cubic centimeters. On December 9, four days after the encephalogram was taken, the basal metabolic rates were minus 11 and minus 9 per cent. On December 10 the calcium of the blood measured 10.6 mg. and the phosphorus 3.8 mg.

Operation and Postoperative Course.—On December 12 a suboccipital craniectomy was performed by Dr. Fay. The tentorium cerebelli was sectioned down to the incisura, and the bulging posterior wall of the third ventricle was opened, allowing the trapped ventricular fluid to escape into the cisterna ambiens. For three days after operation the fluid intake averaged 40 ounces (1,134 cc.) and the output 30 ounces (850 cc.). Then for three days the output was double the intake. On December 19, seven days after operation, high voltage roentgen therapy was started, and the patient received eight daily treatments. The intake and output of fluid gradually balanced at from 40 to 50 ounces (1,134 to 1,418 cc.) and from 45 to 60 ounces (1,276 to 1,701 cc.), respectively. The temperature remained around 98 F. The blood pressure was 110 systolic and 60 diastolic. The basal metabolic rate on the sixteenth postoperative day was plus 11 and plus-minus 4 per cent and on the eighteenth day plus 3 per cent. The cholesterol content of the blood was 277 mg. per hundred cubic centimeters. The dextrose tolerance test on the eighteenth postoperative day showed a value of 100 mg. during fasting, 133 mg. after one-half hour, 180 mg. after one hour, 142 mg. after two hours and 133 mg. after three hours. The patient was discharged on the following day, feeling well, and with instructions to continue the intranasal use of solution of posterior pituitary (pitocin), about 2 cc. every four to six hours.

The patient felt in excellent health for about two and a half weeks. The intake of fluid was about 60 to 70 ounces (1,701 to 1,965 cc.) and the output about 70 ounces per twenty-four hours. He decided to stop the use of pitocin. The output of fluid gradually increased; vomiting began, and he rapidly lost weight and strength. He was readmitted to the hospital on February 5, when he presented a typical picture of marked dehydration. The temperature was 101 F., the pulse rate 90, the respiratory rate 20, the blood pressure 90 systolic and 70 diastolic. The decompression area was markedly depressed. A bilateral Chvostek sign was present. The carbon dioxide–combining power of the blood was 41 cc. per hundred cubic centimeters; the calcium of the blood, 10.4 mg., and the phosphorus, 3 mg. per hundred cubic centimeters; the blood sugar measured 85 mg. and the chlorides 580 mg. The patient responded rapidly to intravenous injection of fluids and dextrose. A second roentgenogram of the skull showed that the pineal gland had returned to its normal position. In repeated studies the basal metabolic rate fluctuated between minus 30 and minus 40 per cent. Intranasal use of pitocin was started, 2 cc. every fourth hour. He gained weight and strength slowly and was discharged on March 22, again feeling well.

He was seen again on May 22, when he was in excellent health. His blood pressure was 110 systolic and 80 diastolic. Strength and appetite were good, and he desired permission to return to work. He stated that he did not have any

more weak spells or hot flashes, that he was now shaving every other day and that libido had returned. He used an average of 25 cc. of pitocin intranasally a month, administering it with an atomizer every six hours. The fluid intake averaged about 75 to 80 ounces (2,207 to 2,268 cc.) and the output about the same. He usually urinated once during the night.

DISCUSSION

DR. TEMPLE FAY: I had no idea that this man had a tumor and have no confirmation yet that one is present, except that on two occasions distortion of the third ventricle was observed. I had considered the probability of an intramedullary lesion because of lack of pressure and absence of the usual signs of tumor. The patient was greatly improved for about three weeks after operation, so that at first I thought the decompression accounted for the change; when he went home, however, the symptoms returned.

DR. F. C. GRANT: It seems curious that the pineal body was pushed down. How does one account for this, when the third ventricle was dilated?

DR. W. E. CHAMBERLAIN: My interpretation is that it was not a tumor but the dilatation of the third ventricle that displaced the pineal gland. That condition is one of the chief means by which one discovers internal hydrocephalus, in which condition I have never seen the pineal body pushed upward. In other words, if the pineal gland is in the midline and is displaced backward and downward, there must be, I think, a suprapineal process. It is important to realize that it is not a tumor, for that would not push the pineal gland down.

INTRACRANIAL ANEURYSMS INVOLVING THE CAROTID ARTERY AND ITS BRANCHES. DR. JOHN H. TAEFFNER.

This is a report of the 9 cases of saccular or arteriovenous aneurysms occurring in Dr. Temple Fay's service at the Temple University Hospital in the past ten years. Cases of aneurysmal dilatation and tortuosity and angioma have not been included.

CASE 1.—E. D., a woman aged 35, during a violent sneezing spell experienced sudden severe pain in both sides of the face, eyes and forehead. There followed a throbbing pain in both eyes; a rapid gain in weight; a bruit in both eyes, more pronounced on the right, which was not entirely stopped by pressure on either carotid artery; exophthalmos with choked disks; dilatation of the conjunctival veins; chemosis; dark red, glossy skin, and an internal squint in the right eye. Ligation of the right common carotid artery had been carried out previously, with temporary benefit, but the condition progressed slowly; ultimately there developed glaucoma and blindness in the right eye, sixteen months after the onset.

CASE 2.—C. K., a woman aged 56, with arteriosclerosis and hypertension, had headache on the right side, with ptosis of the right eyelid; four days later there was left hemiplegia, which disappeared by the following day, when she was admitted with absolute ophthalmoplegia of the right eye, anesthesia in the distribution of the right fifth nerve and a bruit in her head. She died suddenly twelve hours later.

CASE 3.—B. B., a woman aged 47, after an injury to the head, had experienced severe headache, dizziness and roaring in the head (audible on the day of admission); two days later diplopia appeared. On the sixteenth day weakness of the right side of the face developed rapidly, with pain around the left eye, hyperesthesia in the distribution of the left trigeminal nerve and internal squint in the left eye. Six days later the left common, external and internal carotid arteries were ligated, with immediate cessation of the noise. Within a few hours the facial weakness and internal squint had definitely improved. There was rapid improvement for the next three days. On discharge the only disability was double vision on looking to the left. Five years later the patient is working daily and does not have any complaints or diplopia.

CASE 4.—K. M., a woman aged 46, with migraine headaches for twenty-seven years, had had diplopia on looking to the right for one year; six weeks before admission sudden headache developed on the right side, with nausea and dizziness; there were ptosis, hyperalgesia and pain on the right side of the face. She had complete paralysis of the sixth and incomplete paralysis of the third nerve, with diminished corneal sensation in the right eye. A roentgenogram showed a cleancut defect in the mesial part of the right middle fossa. Craniotomy revealed a large, bluish brown, semicystic mass, the nature of which became obvious during an unsuccessful attempt at removal. Death, with hyperpyrexia, occurred two days later. The diagnosis of aneurysm of the carotid artery was confirmed at autopsy.

CASE 5.—J. K., a man aged 41, had had headaches for one year; he had struck his head on a pipe and was staggered; in a few hours there developed vertigo, headache and rapid left hemiparesis, which persisted. There were attacks of crying. Twelve days later he showed left hemiparesis of subcortical type; the upper quadrant of the color field in the left eye was cut; there were awkwardness of the left hand and subnormal temperature. The roentgenogram revealed nothing abnormal. An encephalogram revealed the outline of the tumor. At craniotomy a large, green, solid tumor was removed from deep in the softened right temporal lobe. The pathologic report was that of aneurysm. No clot was found on reexploration for cause of stupor. The patient died on the fourth postoperative day, of respiratory failure. The diagnosis was aneurysm, probably of the middle cerebral artery, at or near its origin.

CASE 6.—M. M., a woman aged 20, after an injury to the head, experienced persistent diplopia, noises in the head and pain in the left side of the face. Six months later the left eye became red and protruding, and the pain in the area of distribution of the left trigeminal nerve was much worse. The left eye showed exophthalmos, complete paralysis of the sixth and partial paralysis of the third nerve and blurred margins of the disk. The left common carotid artery was ligated. On discharge from the hospital, six days later, the patient showed marked improvement in all signs. Noises in the head were present only on lying down. At the time of this report, three and one-half years later, she is reported to be healthy and working—free of all symptoms.

CASE 7.—V. C., a woman aged 51, had had severe headache and migraine for forty years. She fell, striking her head; there followed progressive blindness of the right eye, which was complete, with atrophy of the optic nerve three years later. A year and a half after that she was readmitted for failing vision in the left eye; there were temporal hemianopia and pallor of the disk in that eye. Craniotomy revealed a red, active aneurysm of a branch of the carotid artery, probably the ophthalmic. Decompression was followed by improvement in the visual field.

CASE 8.—G. Y., a man aged 44, was struck on the head with a rock, with resulting fracture of the skull and injury to the left ear. This was followed by a sensation of bells ringing in the left ear and a swishing sound in the right. There were severe frontal headache on the right side, diplopia and extreme weakness. Two and a half years later these complaints persisted; there were paralysis of the external rectus muscle on the right side, a dilated pupil, diminished sensation in the distribution of the trigeminal nerve and pulsation and prominence of the eye, with dilated conjunctival venules. A roentgenogram showed erosion of the right anterior clinoid process from below. The patient signed his own release, and I do not know the subsequent course of the illness.

CASE 9.—E. S., a woman aged 42, experienced a noise in her head after an injury to the head. Two or three months later the noise was increased, and the left eye became prominent and red. Little change occurred for three years, when there was rapid progression. The left eye was markedly exophthalmic, with ectropion, which was pulsating, edematous, fixed and painful. The left common, internal and external carotid and superior thyroid arteries were ligated. There was marked improvement on the following day. On the second postoperative

day improvement continued, but transient hemiplegia appeared on the right, with motor aphasia, light images and zigzags in the right field. The last vestiges of these symptoms disappeared by the following day. On the twelfth postoperative day all signs had practically disappeared; the bruit was entirely gone.

Comment.—In 6 of the 9 cases the condition followed external violence to the head; in 1 it followed internal violence, and in 2 cases there was no record of violence. Arteriosclerosis and hypertension were conspicuous in only 1 case, and there was retinal arteriosclerosis, grade 1, in another. A question of syphilis was present in only 1 case, and this was not confirmed by the history or the clinical laboratory findings. There was a long history of severe, migraine headaches in 2 cases. Seven of the 9 patients were women. Consequently the group appears to be essentially typical.

The high incidence of injury to the head immediately preceding the initial signs, together with the tendency to spontaneous amelioration of signs for varying latent periods and subsequent rapid exacerbation, has led to the following suggestions: (*a*) All patients with post-traumatic disturbance having the not uncommon complaints of tinnitus or dizziness (which includes tinnitus with some patients), headache and double or blurred vision should be examined with a stethoscope as a guide to subsequent management. (*b*) All patients with signs referable to the region of the internal carotid artery should be questioned as carefully for previous injury to the head as for evidence of neoplasm, syphilis or focal infection.

(*a*) In spite of the neurosurgeon's usual suspicion of the nature of encapsulated masses disclosed at operation, better operative results are to be anticipated with a more accurate preoperative diagnosis. (*b*) Ligation at the carotid bifurcation in the neck is of unquestionable benefit when indicated, and the effectiveness generally is in direct relation to the degree of occlusion at the bifurcation. The procedure did not cause any demonstrable persisting untoward signs, though 1 patient was 47 and another 42 years of age.

DISCUSSION

DR. ROBERT A. GROFF: It was not my impression that violence played such a large part in production of intracranial aneurysms. In my experience with aneurysms there has not been as high an incidence of injury to the head. However, it is a point well worth taking.

The operative experiences are interesting. I could add a case to that already mentioned in which a tumor was diagnosed although an aneurysm was anticipated. When an incision was made into the capsule blood was obtained immediately, but it was possible to close the capsule.

DR. L. M. WEINBERGER: I understand that bruits, audible to the observer, are heard with arteriovenous aneurysms. I should like to know if that is the experience of the clinic.

DR. B. J. ALPERS: I wish to ask Dr. Taeffner about these bruits. I have listened over the skull many times in cases in which aneurysms were suspected and later confirmed, but I have never heard a bruit. Is there a particular trick of bringing them out?

DR. TEMPLE FAY: Does Dr. Taeffner ligate the vessels at once, or does he try pressure first to see if that will stop the bruit? I have always had a little hesitancy about ligation. Will Dr. Taeffner describe his technic? Dr. Frazier imbued in me the fear lest some complication such as hemiplegia follow. It has been my practice first to apply two tapes, one around the common carotid and one around the internal carotid artery. With the tapes in place, which are well waxed or oiled so that there will be no cutting of the arterial coat, I then exert gradual pressure on the common carotid artery, and during that time I ask the anesthetist to watch for a change in respiration and pulse. The patient, having only a local anesthetic, is required to move the face and hands for two or three minutes before the tape is tied. The internal carotid artery provides a blood

supply, so that there is not a complete shut-off at the moment of tying. Next, the internal carotid artery is tied, and of course the external carotid can be tied at any time. The procedure takes about half an hour and is not without great anxiety. In 1 case the procedure was carried out without the development of any symptoms, but on the third day the patient had aphasia and hemiparesis. It disappeared in forty-eight hours, but I did not think it would. Again, I used my method of dehydration. Whether it was of value I do not know. In another case I was not as clever as Dr. Groff, but removed an aneurysm. When the specimen was sent to the laboratory, the question was asked: "Since when have you removed aneurysms of the third ventricle?" The aneurysm did not pulsate because the wall was so thick.

Dr. John H. Taeffner: It is difficult to find from the literature how to differentiate between an arteriovenous and a sacculated aneurysm. One cannot expect to determine which one will eventually rupture.

A bruit is difficult to hear in any case, although one more or less acquires the knack of detecting it. When the stethoscope is first placed over the eye nothing is heard, except possibly a little roaring. If a patient hears a bruit, one may perhaps hear it oneself.

Dr. Temple Fay: Dr. Taeffner taught me to recognize the high note that is observed in the case of a small aneurysm. After having it pointed out once and hearing it, and then waiting until the patient relaxes and one relaxes oneself, with nothing touching the stethoscope, one will hear what I am sure I missed before. It can be amplified by the audioamplifier, and one can pick out the best zones for obtaining it. There is a small high note that escaped me entirely until Dr. Taeffner pointed it out; since, I have been able to find it without Dr. Taeffner's assistance.

Treatment of Exophthalmos by Decompression of the Orbit: Report of Two Cases. Drs. Augustus McCravey and Homer R. Mather Jr. (by invitation).

There follows a report of 2 cases of malignant exophthalmos treated by decompression of the orbit. One case affords an opportunity for comparing the Naffziger with the Swift operation.

Case 1.—E. M., a woman aged 34, three months after thyroidectomy experienced painful, prominent eyes with congestion and mucoid secretion. Dr. I. Lillie advised decompression of the orbits, but the patient did not return until two months later, when the bulbar conjunctiva protruded between the lids. Movements were limited in all directions. Vision was poor; there was bilateral keratitis, and the exophthalmos measured 33 mm. on the right and 32 mm. on the left.

A bilateral Naffziger operation was performed on Aug. 9, 1935 by Dr. Temple Fay. A transverse incision was made across the vertex just behind the hair line, from one temporal region to the other. The scalp was reflected forward over the frontal bone down to the supraorbital ridge. A bilateral bone flap was reflected, the temporal muscle being used as a hinge. A small ridge of bone was left intact in the midline over the superior longitudinal sinus. The dura was elevated and retracted from the roof of the orbit. The orbital roof, including the roof of the optic foramen, was removed with a rongeur. The orbital fascia and the ring of Zinn were opened. The ocular muscles were enormously enlarged, the thickness being about four to six times that of the normal. A similar procedure was carried out on the opposite side. Bone flaps were replaced, and the galea and skin were closed with separate sutures of silk.

Clinical Course.—There was evidence of gross improvement immediately after the operation. The lids were less tense, and the eyes had receded slightly into the orbits. Recovery from operative procedures was rapid and uneventful. The corneas were still exposed, and Dr. Lillie performed bilateral canthotomy and blepharorrhaphy on two occasions.

Two weeks after discharge from the hospital the patient returned with more advanced keratitis and a subsequent perforation of the cornea of the right eye and total blindness in that eye. The cornea of the left eye was vascularized, and vision was retained only for moving objects.

Two years after decompression of the orbits the right eye protruded 24 mm. and the left 21 mm. Vision in the left eye was good for moving objects and color. Vision was still improving in the left eye at the last examination, on Jan. 9, 1939.

Case 2.—B. B., a man aged 38, was referred by Dr. C. J. Ulshafer, of the Locust Mountain State Hospital, Shenandoah, Penn., to Dr. Temple Fay's service at Temple University Hospital on July 8, 1938. After thyroidectomy the signs of hyperthyroidism disappeared, but protrusion of the eyes became worse until the time of admission ten months after thyroidectomy; the patient complained of severe headache beginning behind the eyes and radiating to the occipital region. There were also diplopia and blindness of the temporal fields bilaterally, with burning and excessive lacrimation.

The eyelids were full and puffy; exophthalmos measured 26 mm. in each eye at a distance of 116 mm. The von Graefe sign was present. There was limitation of movements laterally and superiorly. There was congestion of the conjunctiva where it was exposed between the lids. The pupils were about 7 mm. in diameter and reacted to light and in accommodation. There was physiologic fulness of the disks, with suggestion of papilledema on the right side.

The Swift operation was performed on the right eye by Dr. Temple Fay on Aug. 16, 1938. A semicircular incision, about 5 cm. long, in the lateral region of the right orbit, and a horizontal incision, about 3 to 4 cm. long, extending back to the temporal region, were made. The orbicularis oculi muscle was retracted anteriorly, and the temporal muscle was retracted posteriorly, exposing the lateral margin of the orbit and the temporal fossa. The periosteum was dissected free from this portion of the bone, both on the orbital and on the temporal surface, and about 3 cm. of the lateral bony arch was removed with a rongeur. As the temporal muscle and periosteum were retracted, the lateral wall of the orbit and a part of the great wing of the sphenoid bone were removed with the rongeur, giving decompression of the orbit and supraorbital fissure into the temporal and middle fossae. Likewise, the orbital roof was removed anteriorly almost to the frontal sinuses, medially almost to the ethmoid sinuses and posteriorly to the sphenoid ridge and anterior clinoid process, giving full decompression of the optic foramen. The orbital fascia, including the ligament of Zinn, was opened in all directions, allowing free decompression of the orbital contents, which bulged in the bony opening when the capsule was opened. No severe bleeding was encountered, and hemostasis was easily produced. The superficial periosteum, fascia and skin were closed in separate layers with interrupted silk sutures.

Immediately after the operation the globe of the eye had definitely receded into the orbit.

The Naffziger operation, previously described, was performed on the left side, nine days after the Swift operation on the right.

Clinical Course.—Recovery from both operative procedures was rapid and uneventful. However, convalescence was much shorter after the Swift than after the Naffziger operation. There was a noticeable improvement in the exophthalmos, edema, congestion of the lids and movements of the eye immediately after the operative procedures. About five months later the exophthalmic reading for the right eye was 22 mm. and for the left eye 22.5 mm., at a distance of 114 mm. The edema and congestion had subsided; the external movements of the eyes were still improving, and the occipital headaches had disappeared completely. Vision was 6/10 in both eyes.

Comment.—The first case illustrates the fallacy of delay in decompression of the orbit in cases of progressive exophthalmos. Early decompression of the orbits would have preserved useful vision in both eyes. In the second case, in which the exophthalmos measured the same in both eyes, a different operative approach was

used for each eye. This afforded an excellent opportunity to observe the relative merits of the two procedures, and the case is the first to be reported in which treatment has been carried out in this manner. The results to date have been equally satisfactory. However, the Swift operation was less formidable, the operating time being about one-half that of the Naffziger operation and convalescence was shorter.

It was interesting to note that in both cases the exophthalmos progressed rapidly after thyroidectomy; however, the toxic signs disappeared.

The extraocular muscles in both cases showed extreme hypertrophy, as has been described by others.

DISCUSSION

Dr. F. C. Grant: I have not had the opportunity to decompress an orbit for exophthalmos accompanying disease of the thyroid, but I have done this in 3 cases of intraorbital tumor. About three weeks ago, I decompressed an orbit because I could not account for the exophthalmos except on the basis of an intraorbital tumor. The operation by an intracranial approach, with removal of the orbit, is simple to carry out. I have not performed the Swift operation, so I cannot speak from personal knowledge. The Naffziger approach affords an excellent view of the orbital content. The orbital canal can be opened without particular difficulty, and my impression is that the cosmetic effect is better than from the Swift approach. The only time I have seen the lateral approach used was in an operation performed by Dr. Edmund Spaeth, of the Graduate Hospital, for an intraorbital tumor, and it did not seem to me to be as adequate as the approach from above, because one could see only the lateral portion.

From my personal experience, I prefer to perform the Naffziger rather than the Swift operation; certainly, in cases in which there is hypertrophy of the muscle it is possible by that procedure to secure a satisfactory contraction of the orbital content. It seems to me to be an operation that should be performed more frequently.

Dr. W. I. Lillie: This seemed to be an excellent case in which to compare what might be obtained by the Swift and by the Naffziger approach. In this case the end result of each operation has been similar. There was no corneal complication, and I feel sure the patient's sight has been saved.

In cases of exophthalmos which develops while the toxic goiter is still present, the exophthalmos rarely, if ever, progresses to a malignant form after thyroidectomy. In all these cases the condition is found in persons with a high basal metabolic rate at the time the thyroid is removed. After the operation this drops to plus 5 per cent or even lower. I think it is the sudden change in metabolic rate which causes the trouble. The swelling of the muscles speaks for that rather than for any other cause. This has not been proved from a clinical standpoint, but it seems that this may be the basis for the development of the exophthalmos after the surgical procedure.

Dr. B. L. Keyes: It would be of interest to examine the records in cases of exohthalmos to see if there had been partial thyroidectomy or ligation in any of them, or whether the thyroidectomy had been a single stage subtotal operation.

Dr. Augustus McCravey: In neither of the present cases had ligations been performed previous to the operative procedure. These cases verify the opinion of Dr. F. C. Grant and other authorities that it is important to perform the operation for decompression before vision is gone.

Probable Significance of Streptococcic Viridans in Certain Neurologic Manifestations. Dr. G. A. Esslinger.

Certain ill defined neurologic disorders have attracted the interest of Dr. Temple Fay and his staff at the Temple University Hospital. In the past ten to eighteen years, the literature carried reports of similar cases under such a variety of diag-

noses as the Guillain-Barré syndrome, acute infectious polyneuritis, radiculitis, acute infectious meningomyeloneuritis, myeloradiculitis, thrombophlebitis of the meningorachidian veins and even Landry's ascending paralysis.

Strauss and Rabiner (Myeloradiculitis: Clinical Syndrome, with Report of Seven Cases, ARCH. NEUROL. & PSYCHIAT. **23**:240 [Feb.] 1930) stated: "Almost all cases have a history of upper respiratory infection." This was found to be true of the cases studied in the Temple University Hospital. Because of this and the suspected inflammatory lesions in the meningorachidian veins, a survey of five major services at Temple University Hospital with respect to the type of bacteria recovered from the nasal and oral passages was made. By so doing, it was believed that data might be obtained which would show a correlation between the bacterial cultures and the clinical syndromes and henceforth serve as a crude index in determining an etiologic factor in these ill defined neurologic disorders.

A table represents the results of the study of 651 cultures from neurologic, medical, pediatric, nose and throat and orthopedic services. Material was taken from the nose, throat, nasopharynx, gums and sputum only. The data were taken from the regular records of the department of bacteriology for 1938. No attempt at differential culture was made. Results of culture were recorded only when colonies appeared in numbers pathologically significant. Unverified types of bacteria and counts of occasional, few or moderate numbers of colonies were not used. In some cultures more than one organism appeared in pathologic numbers. These were recorded.

The percentages of pathologically significant organisms were arrived at by comparing the number of positive cultures for each type of organism with the total number of cultures made in each service. Of a total of 651 cultures for the five services surveyed, 201 were from the neurologic, 190 from the medical, 130 from the pediatric, 93 from the nose and throat and 37 from the orthopedic service. The types of organisms found to be significant were Streptococcus viridans, hemolytic streptococci, nonhemolytic streptococci, hemolytic Staphylococcus aureus and pneumococci. All the types of organisms but Str. viridans showed percentages of no wide variation, and therefore of little significance in connection with neurologic disorders.

The percentages for Str. viridans, on the other hand, were found to vary widely for the five services, as follows: neurologic, 61; medical, 40; pediatric, 35; nose and throat, 27, and orthopedic, 73.

Analysis of these percentages reveals interesting evidence. First, the variation is too great to consider Str. viridans as an organism of no pathologic significance. The percentages in the medical and the pediatric department are about the same: 40 and 35, respectively, as might be expected in two rather parallel medical service.

Of special interest is the low figure of 27 per cent for the nose and throat service, which again throws doubt on the possibility of Str. viridans being considered a universally normal organism.

The high percentage of Str. viridans in the orthopedic service may be regarded with suspicion, since the total number of cultures taken was only 37, and hence was too small to be of value. On the other hand, cultures were taken only in cases in which the conditions were not clearcut orthopedic entities, but presented problems in low back pain, sciatic syndromes and questionable arthritis and neuritis.

The incidence of Str. viridans of greatest significance is the 61 per cent occurring in the neurologic service. It is also noteworthy that the lowest percentage of all the other types of organisms considered occurred in the neurologic services.

In conclusion, this survey of bacterial cultures from five different services suggests that Str. viridans may be a pathogenic organism worthy of note in cases of neurologic complaints. Furthermore, if this can be proved to be true, the data here accumulated may indicate that culture of the nasal and oral passages would

be an aid in determining the etiologic factor in diseases of the tissues and vessels of the central and peripheral nervous system.

DISCUSSION

DR. E. H. SPALDING: This paper reveals several points of particular interest to bacteriologists. The first is the apparent relationship between the increased frequency of Str. viridans in the throat and gums, where they are commonly found, and the neurologic manifestations. However, it shows that in the instances in which the percentage of Str. viridans was definitely increased there may have been some correlation. In cases of oral sepsis Str. viridans increases tremendously. In some circumstances the organisms gain access to the blood stream, and, although normally they rapidly disappear, in patients in whom there is sensitization they may persist. There is an increasing number of reports in the literature at present attributing various vascular lesions to Str. viridans.

If the process is infectious it would be surprising if the only organism were Str. viridans. Other types of streptococci may well produce the same pathologic change.

DR. G. A. ESSLINGER: Tissue studies formed part of the report included in Dr. Fay's article (*Confinia neurol.* **1**:93, 1938). The tissue was said by the pathologist to show evidence of inflammation. That has occurred in a number of cases besides those reported. In 1 case there was an interesting correlation. Study of the gums, nose and throat failed to reveal any significant pathologic changes, but a pure culture of Str. viridans was obtained from the antrum. About five days after the culture was made, thrombophlebitis developed in one leg.

Book Reviews

Nursing Mental Diseases. By Harriet Bailey, R.N. Fourth edition, revised. Price, $2.50. Pp. 264. New York: The Macmillan Company, 1939.

The first edition of this book appeared in 1920. The present edition contains an excellent glossary and a comprehensive bibliography, which contribute much to the usefulness of the book. The subject matter has been rearranged to conform to the revised classification of mental disorders adopted by the American Psychiatric Association, and takes cognizance of the fact "that the nursing of psychiatric patients depends more upon individual reactions due to personality and behavior than diagnosis."

In the preface the author states that, in response to many suggestions received, an attempt has been made to include "more descriptions of nursing procedures, more information as to what to say and do, and more concrete suggestions for approaching the patient and establishing the necessary rapport." The result is praiseworthy. A valuable contribution is the part of the book which deals with symptoms and their observations. Here the important point is made "that it cannot be too frequently brought to the attention of the nurse that in recording or reporting symptoms she should state exactly what is said or done rather than what condition she thinks the symptoms indicate." In the chapters devoted to the representative types of psychoses, the author has successfully brought about an integration of the principles of psychiatry with those of psychiatric nursing. In these chapters the significant role of the nurse is clearly emphasized, and important points are illustrated by citation of concrete examples. Insulin therapy and metrazol therapy are treated too briefly and too generally to be of much use.

The author's keen insight and common sense are shown throughout the book. In the section in which the "Qualifications for Mental Nursing" are discussed, she aptly says: "In the nursing of the mentally ill every bit of personality counts, every bit of intelligence counts and every bit of insight as to what is going on in the patient's mind counts. The psychiatrist directs the way; to the nurse is the responsibility of leading the patient back to health." The topics hydrotherapy, occupational and recreational therapy and psychotherapy are dealt with in a practical manner. The chapter on "Mental Hygiene" is good.

Because of its practical, concise and inclusive treatment of the various phases in the field of psychiatric nursing, this book should serve as an excellent tool in the hands of students, who must cover so much material within the short period of a few months allotted to this important subject. It would seem, however, that material adequately treated in other courses might well have been left out, for example, tube feeding, treatment of fractures and burns.

The Control of the Circulation of the Blood. By R. J. S. McDowall, G. E. Malcomson and I. McWhan. Price, $22.50. Pp. 619, with 38 illustrations. New York: Longmans Green & Co., 1939.

Not since 1923, when Tigerstedt published his great work on the physiology of circulation, has anybody made the attempt to review completely the literature in this important field. McDowall has undertaken this task with regard to the control of circulation. The work has an extensive and reliable bibliography of about 7,000 references. The book is chiefly concerned with an analysis of the nervous factors in the control of circulation, but the hormonal control, particularly by epinephrine, is discussed also in great detail. The exhaustive review of the literature makes the work extremely valuable to the investigator interested in neurocirculatory mechanisms. Detailed study of the book, however, is disappoint-

ing. The author has not been able to guide the reader through the vast literature, but seems satisfied to list the various, and often conflicting, results. Proper evaluation of the buffer mechanisms in the carotid sinus and the arch of the aorta would have contributed greatly to such a clarification.

The Occupational Treatment of Mental Illness. By John Ivison Russell, M.B., Ch.B., F.R.F.P.S. (Glasg.), D.P.M. With foreword by William Rees-Thomas, M.D., B.S., F.R.C.P. (Lond.), D.P.M. (Camb.). Price, $2.50. Pp. 247, with 41 illustrations by Joseph Blagdon Morgan. Baltimore: William Wood & Company, 1938.

This book has been prepared primarily with the instruction of nurses in mind. It is divided into two parts, the first dealing with simple statements of psychologic types of persons, forms of mental illness, the prescribing of occupation according to the effects desired and the organization of occupational and recreational activities in an institution. The second part of the book will be found of particular value in that it gives practical directions concerning many kinds of occupation. It should be useful not only to nurses but also to physicians in hospitals for mental disease, who usually have had little experience in handwork that has been proved useful in the occupational treatment of patients.

Report on Cardiazol Treatment and on Present Application of Hypoglycaemic Shock Treatment in Schizophrenia. By W. Rees Thomas, M.D., and Isabel G. H. Wilson, M.D. Price, 30 cents. Pp. 70. London: His Majesty's Stationery Office, 1938.

In 1937 Dr. Wilson published a pamphlet which dealt chiefly with the hypoglycemic treatment. Metrazol therapy was but briefly sketched. In the present pamphlet both procedures are surveyed fairly exhaustively and are reviewed critically. Like the publication of the preceding year, the 1938 review is a matter-of-fact record, crowded with tables and compact with well chosen verbatim quotations. The literature is ably covered; the discussion is detached but sympathetic; the presentation is clear and fluent. As a condensed account of the present status of shock therapy the booklet will serve a useful function.

News and Comment

THE AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The seventeenth annual meeting of the American Orthopsychiatric Association, an organization for the study and treatment of behavior and its disorders, will be held at the Hotel Statler, Boston, on Feb. 22, 23 and 24, 1940. The secretary is Dr. Norvelle C. La Mar, 149 East Seventy-Third Street, New York.

Notices

CUMULATED INDEX OF THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY

Requests have been received for a twenty year index of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $6 per copy; that is, whether one thousand copies could be sold. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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